Relations of magnesium intake to cognitive impairment and dementia among participants in the Women's Health Initiative Memory Study: a prospective cohort study

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ABSTRACT

Objective To examine the associations of dietary and supplemental magnesium (Mg) as assessed by a semi-quantitative food frequency questionnaire with cognitive outcomes among ageing women.

Design This work conducts a prospective cohort study of participants enrolled in the Women's Health Initiative Memory Study (WHIMS), which was subsequently extended and named WHIMS-Epidemiology of Cognitive Health.

Setting Forty clinical centres in the USA.

Participants Postmenopausal women aged 65–79 years without dementia on enrolment.

Main outcome measures Physician-adjudicated mild cognitive impairment (MCI) and/or probable dementia (PD).

Results Participants were excluded (n=1006) if they had extreme values of dietary energy intake, had missing or extreme body mass index values, with prevalent MCI/PD at baseline, received only one cognitive assessment or had been followed up for <1 year. During >20 years of follow-up, 765 (11.8%) out of 6473 participants developed MCI/PD. For MCI/PD and MCI, the risks tended to be lower among participants in quintiles Q2–Q5 of Mg consumption compared with those in the lowest quintile. Participants in Q3 had a significantly lower risk of MCI/PD (HR 0.69, 95% CI 0.53 to 0.91) and MCI (HR 0.63, 95% CI 0.45 to 0.87) after multivariate adjustments. No significant association was observed between total Mg intake and PD. The association between total Mg intake, MCI/PD and MCI was non-linear as suggested by the likelihood test.

Conclusions Total Mg intake between the estimated average requirement and the recommended dietary allowances may associate with a lower risk of MCI/PD and MCI.

Trial registration number NCT00685009.

Strengths and limitations of this study

► A large prospective cohort with long follow-up and careful adjudication of mild cognitive impairment/probable dementia events to ensure a high quality of outcome assessment.
► Lacking information on serum magnesium levels in the studied population.
► The cohort included only postmenopausal women, and the findings may not be generalisable to elderly men.

enough to interfere with her or his daily activities.[1] Cognitive function might decline progressively over time for people with MCI, which would impair their memory, reasoning, language and visuospatial abilities. Individuals are diagnosed with dementia when their cognitive decline interferes with their daily functions.[2] Dementia affects approximately 47 million people worldwide, and its prevalence is expected to be more than triple by 2050.[3] The prevalence of dementia and associated medical costs have increased dramatically in recent years in parallel with the ageing population throughout the world; this situation has increased the healthcare burden to communities, families and individuals.[3] Compared with elderly men, elderly women have a higher lifetime risk for dementia[4 5] and faster progression of cognitive impairment following diagnosis.[6] Therefore, identifying the strategies for dementia prevention, particularly those that are safe, cost-effective and readily accessible to elderly women, is of both public health and clinical significance.

Magnesium (Mg) has long been thought to prevent vascular outcomes. Recent work has shown that Mg may regulate

BACKGROUND

Mild cognitive impairment (MCI) involves the onset and evolution of cognitive impairments beyond those expected based on an individual's age and education but not significant

N-methyl-D-aspartate (NMDA) receptors, which affect critical functions of the central nervous system, including neuronal development, plasticity and neurodegeneration. The NMDA receptor is permeable to calcium, sodium and potassium ions and can be blocked by Mg ions.[7] Strong neurobiological data support the role of Mg intake for normal neuron functioning by helping prevent the destruction of neurons resulting from NMDA-induced excitotoxicity.[8] However, few prospective studies have directly examined the relation between Mg intake (dietary and/or supplements) and the dementia risk.[9 10] We therefore conducted a prospective investigation of the role of Mg intake in the development of two constructs of cognitive decline, namely, MCI and probable dementia (PD), among elderly women who participated in the Women's Health Initiative Memory Study (WHIMS; 1995–2008). The participants were also followed up in the WHIMS-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO; 2008 onwards) study.

METHODS

Data source

WHIMS is an ancillary study to the WHI Hormone Trial (n=27 347 for the whole trial) designed to assess the effect of postmenopausal hormone therapy (HT) on dementia risk.[11] Invitation to participate was sent to women in the WHI Hormone Therapy Trial; these women were aged 65–79 years and did not have dementia on enrolment.[12] Following the termination of the HT intervention, WHIMS (1995–2008, 7479 participants) and subsequent WHIMS-ECHO follow-up (2008 onwards, ~2900 participants) continued the annual assessments of cognitive function and adjudication of all-cause dementia and MCI status. Written informed consent was obtained from the participants.

The participants were eligible for inclusion in the present analysis if they completed the WHI Food Frequency Questionnaire (FFQ) and dietary supplement questionnaire at baseline. We further excluded women who had implausible dietary energy intake (<600 or >5000 kcal), missing or extreme body mass index (BMI) values (BMI <15 or >50 kg/m^2) and prevalent MCI/PD at baseline or received only one Modified Mini-Mental State Examination (3MSE) for cognitive assessment. Lastly, to avoid reverse causation between the dietary intake and disease onset, we included only women who had been followed up for at least 1 year. The detailed participant selection is illustrated in online supplementary figure 1.

Outcome variable

The WHIMS and WHIMS-ECHO protocol used a multiphase approach to identify cases of MCI and PD. From 1995 through 2007 (WHIMS), participants were screened annually in the clinic by trained and certified examiners by using the 3MSE. The 3MSE ranges from 0 to 100, and the initial cut-points for further testing were 72 or below for participants with <9 years of education and 76 or below

for participants with 9 years or above of education. After 1 July 1998, the cut-points were 80 and 88, respectively. Participants who scored below the education-adjusted 3MSE cut-points received in-depth multiphased evaluation,[13] including a battery of neuropsychological tests, history and physical, neuropsychiatric evaluation and an interview with a friend or family member to assess the functional status.[11]

Beginning in 2008 (WHIMS-ECHO), an annual validated cognitive test battery that included the Telephone Interview for Cognitive Status-modified (TICSm) was conducted.[14] Other validated tests of cognitive function were administered by telephone.[15] To justify replacing the 3MSE assessment with TICSm, a validation study was performed. The results showed that the 3MSE scores predicted by TICSm was highly correlated (0.82) with 3MSE scores,[16] whereas the transformation of WHIMS 3MSE and WHIMS-ECHO TICSm data into relative percentile ranks fit the trajectories of global cognitive function.[17] For women screened positive (ie, TICSm <31) during the WHIMS-ECHO follow-up, a reliable and preidentified informant was interviewed via telephone by using the standardised Dementia Questionnaire to assess the history of cognitive and behavioural changes, functional impairments and health events that can affect cognitive functioning.[18]

All available participant data in both WHIMIS and WHIMS-ECHO were submitted to a central adjudication committee at the WHIMS clinical coordinating centre. The committee had experts experienced in neurological examinations and neuropsychiatric evaluations, wherein cases are classified as no impairment, MCI or PD.[19] The outcome classification was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for dementia[20] and Petersen's MCI criteria.[1]

Exposure variable

The dietary Mg intake at baseline was derived using the baseline WHI semi-quantitative FFQ.[21] The nutrient database for the WHI FFQ uses the Nutrition Data Systems for Research (NDS-R, V.2005, University of Minnesota Nutrition Coordinating Center, Minneapolis, Minnesota, USA) food and nutrient database.[22] The data on the current dietary supplements at baseline were assessed by a special dietary supplement inventory interviewer-administered questionnaire.[23] Participants were asked to bring all current supplements to the WHI baseline clinic visit. Staff members directly transcribed the ingredients for each supplement; the result demonstrated high correlation (ranging from 0.8 to 1.0) with photocopied labels in the validation study.[24] Total Mg intake was calculated by the summation of dietary and supplemental Mg intake. To test the relationship between total Mg intake and MCI/PD, the Mg intake levels were categorised into quintiles.

Covariates

At WHI baseline, WHIMS participants completed the questionnaires on various information, including demographics

(age and race/ethnicity), socioeconomic status (education in years), lifestyle factors (diet, smoking, alcohol use and physical activity), family or personal disease history (family history of diabetes or heart diseases, personal history of diabetes, heart diseases, cancer or related risk factors) and medication use (use of anti-inflammatory drugs, antihyperlipidaemia drugs, antidepressants, antihypertensive drugs or diuretics). Height and weight were measured at baseline to calculate the BMI.

Data analysis

Descriptive statistics were demonstrated by the quintiles of total Mg intake. The differences between quintiles were tested by one-way analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. To examine the relationship between total Mg intake and incident MCI and/or PD, Cox proportional hazards regression models were used with results presented as HRs and associated 95% CIs. Non-cases were censored at the time of the last follow-up (WHIMS or WHIMS-ECHO), death or at the end of 2012 (the year with the most updated data from WHIMS-ECHO), whichever came first. With reference to the common analysis strategies of other WHIMS studies,[25–27] the MCI/PD end point was presented as a combined end point in the primary analyses. MCI and PD were treated as secondary end points. The event time was defined as the time of screening by global cognitive tests (either 3MSE or TICSm) that triggered the subsequent workup that concluded with the central adjudication of first MCI/PD. If a participant had progressed from MCI to PD, then she was classified as a case of PD instead of MCI. The test for linear relationship was conducted by assigning median values for quintiles and then treated it as a continuous variable in the regression model. To examine the potential non-linear relationship between the Mg intake (total intake or from diet only) and cognitive decline, we conducted a likelihood ratio test to compare the fit of continuous models with or without quadratic terms of Mg intake. A likelihood test with p<0.05 would suggest a better fit regression model by including the quadratic term. Thus, a non-linear relationship between the Mg intake and cognitive outcomes was determined. To test the assumption of the Cox proportional hazards model, we examined all models by using the Schoenfeld residual test. A sensitivity analysis was performed by using dietary Mg intake only.

To ensure robustness of the regression analysis, we controlled for confounders with reference to previous studies on cognitive decline. Model 1 was the minimally adjusted model and included age at baseline, region in the USA, race/ethnicity, assignment arm of HT trial, BMI at baseline[28] and smoking status.[29] Model 2 involved covariates in model 1 plus education,[30] dietary variables and physical activity (alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin $B_6/B_9/B_{12}$, total

intake of calcium and vitamin D, dietary energy in kcal),[27 31–34] the medical history and medication use (baseline self-reported status of diabetes identified by the question "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?"),[35] cardiovascular disease (including cardiac arrest, congestive heart failure, cardiac catheterisation, coronary bypass surgery, angioplasty of coronary arteries, carotid endarterectomy/angioplasty, atrial fibrillation or aortic aneurysm),[36] cancer (except for skin melanoma),[37] prior use of menopausal replacement therapy,[38] personal history of hypertension,[39] personal history of high cholesterol requiring medications,[40] family medical history of diabetes, family history of heart attack or stroke and medication use (anti-inflammatory drugs, antihyperlipidaemia drugs, antidepressants, antihypertensive drugs or diuretics at baseline).[41 42] Only participants with complete data were included in each regression model. All statistical analyses were performed with R V.3.6.0. P values <0.05 were considered to be statistically significant.

Patient and public involvement

No patients were involved in the design of this study, in the setting of the research question or the outcome measures nor were they involved in the analysis, interpretation and writing of the results. With regard to the long follow-up period, dissemination to these groups is not applicable.

RESULTS
Participant characteristics

A total of 6473 participants were included in the analyses. The baseline characteristics of participants in WHIMS by quintiles are presented in table 1. Women in the highest quintiles of Mg intake tended to have, on average, a longer time to event/censorship, greater energy expenditure from recreational physical activity and higher levels of all dietary variables as shown by one-way ANOVA. As demonstrated by the χ^2 test, non-Hispanic white women, participants enrolled in the control group of the oestrogen+progestin trial, consumed ≥7 alcohol drinks per week, with a history of cardiovascular disease, were former smokers or receiving postcollege education were more likely to have a higher level of Mg intake. The baseline characteristics of participants included (n=6473) or excluded (n=1006) from the analysis are compared in online supplementary table 1. Between-group difference was significant for the majority of variables except for baseline age, recreational physical activity, total B_6 and B_{12} intake, prevalent cancer, use of hormonal replacement therapy, treated high cholesterol and family history of diabetes/heart attack/stroke.

Total magnesium intake and risk of MCI/PD

Table 2 illustrates the association between total Mg intake and risk of MCI and/or PD. Five-hundred and five (7.8%)

Table 1 Baseline characteristics of participants in the women's health initiative memory study by quintiles of total mg intake

	Mean (SD)/N (%)					
	Q1 (<197.4 mg/day)	Q2 (197.4–257.3 mg/day)	Q3 (257.3–317.8 mg/day)	Q4 (317.8–398.7 mg/day)	Q5 (>398.7 mg/day)	P value
Number of participants	1294	1295	1295	1295	1294	
Time-to-event/censored in years	9.1 (4.4)	9.6 (4.3)	9.9 (4.3)	9.8 (4.3)	9.7 (4.4)	***
Age at baseline in years	69.9 (3.7)	70.1 (3.8)	70.1 (3.8)	70.1 (3.9)	70.2 (3.9)	NS
BMI at baseline	28.6 (5.5)	28.5 (5.3)	28.3 (5.4)	28.3 (5.3)	28.3 (5.5)	NS
Recreational physical activity in MET-hour	9.4 (12.4)	10.5 (12.2)	11.2 (12.9)	12.3 (13.2)	13.3 (14.9)	***
Total magnesium intake in mg	153.7 (29.9)	228.2 (17.7)	287.1 (17.6)	355.3 (23)	531.1 (172.3)	***
Total $B6_6$ intake in mg	3.7 (20.3)	5.1 (22.7)	5.7 (18.2)	6.9 (21.2)	12.9 (47.6)	***
Total $B9_9$ intake in µg	219.2 (144.3)	349.5 (227.7)	451.3 (195.4)	569.3 (215)	698.8 (278.9)	***
Total $B12_{12}$ intake in µg	12 (54.5)	17.3 (83.7)	16.2 (51.9)	19.5 (54.8)	37.3 (102.9)	***
Total calcium intake in mg	632.9 (632.6)	877.6 (459.3)	1091.1 (537.7)	1335.8 (566.8)	1758.9 (686.7)	***
Total vitamin D intake in µg	3.9 (3.9)	6.7 (4.8)	9.4 (5.3)	11.8 (5.4)	15.5 (7.1)	***
Dietary energy in kcal	1080.1 (306.1)	1375.4 (365)	1589.4 (444.6)	1845 (537.6)	2135.7 (758)	***
Region in the USA						
Northeast	336 (26.0%)	377 (29.1%)	365 (28.2%)	333 (25.7%)	360 (27.8%)	NS
South	278 (21.5%)	264 (20.4%)	255 (19.7%)	280 (21.6%)	238 (18.4%)	
Midwest	310 (24.0%)	310 (23.9%)	316 (24.4%)	349 (26.9%)	313 (24.2%)	
West	370 (28.6%)	344 (26.6%)	359 (27.7%)	333 (25.7%)	383 (29.6%)	
Race/Ethnicity						
Non-Hispanic white	1040 (80.6%)	1121 (86.7%)	1160 (89.6%)	1194 (92.4%)	1168 (90.5%)	***
Black or African-American	139 (10.8%)	94 (7.3%)	70 (5.4%)	45 (3.5%)	67 (5.2%)	
Hispanic/Latino	52 (4.0%)	32 (2.5%)	23 (1.8%)	15 (1.2%)	22 (1.7%)	
Other	59 (4.6%)	46 (3.6%)	41 (3.2%)	38 (2.9%)	33 (2.6%)	
HRT arm						
E-alone	285 (22.0%)	291 (22.5%)	247 (19.1%)	198 (15.3%)	227 (17.5%)	***
E-alone control	286 (22.1%)	241 (18.6%)	225 (17.4%)	248 (19.2%)	257 (19.9%)	
E+P intervention	359 (27.7%)	374 (28.9%)	402 (31.0%)	414 (32.0%)	386 (29.8%)	
E+P control	364 (28.1%)	389 (30%)	421 (32.5%)	435 (33.6%)	424 (32.8%)	
7+ alcohol drinks per week	116 (9.0%)	151 (11.7%)	161 (12.5%)	191 (14.8%)	191 (14.8%)	***
Prevalent diabetes	107 (8.3%)	112 (8.7%)	92 (7.1%)	93 (7.2%)	103 (8.0%)	NS
Prevalent cardiovascular disease	196 (15.4%)	236 (18.5%)	212 (16.6%)	198 (15.5%)	241 (18.8%)	*
Prevalent cancer	54 (4.2%)	42 (3.3%)	43 (3.3%)	50 (3.9%)	43 (3.3%)	NS
HRT						NS
Never used	878 (67.9%)	913 (70.5%)	885 (68.3%)	885 (68.3%)	883 (68.2%)	
Past user	353 (27.3%)	318 (24.6%)	329 (25.4%)	334 (25.8%)	323 (25%)	
Current user	63 (4.9%)	64 (4.9%)	81 (6.3%)	76 (5.9%)	88 (6.8%)	
Treated high cholesterol	220 (17.3%)	239 (18.7%)	245 (19.1%)	222 (17.4%)	225 (17.5%)	NS
History of hypertension	497 (38.9%)	528 (41.1%)	498 (38.7%)	455 (35.5%)	514 (40.0%)	NS
Family history of diabetes, heart attack or stroke	983 (76.0%)	999 (77.1%)	1024 (79.1%)	1003 (77.5%)	982 (75.9%)	NS
Medication use†	594 (45.9%)	610 (47.1%)	592 (45.7%)	592 (45.7%)	621 (48.0%)	NS
Smoking status						***
Never smoked	689 (53.2%)	691 (53.4%)	707 (54.6%)	663 (51.2%)	696 (53.8%)	
Past smoker	488 (37.7%)	500 (38.6%)	509 (39.3%)	566 (43.7%)	534 (41.3%)	
Current smoker	117 (9.0%)	104 (8.0%)	79 (6.1%)	66 (5.1%)	64 (4.9%)	

Continued

Table 1 Continued

	Mean (SD)/N (%)					
	Q1 (<197.4 mg/day)	Q2 (197.4–257.3 mg/day)	Q3 (257.3–317.8 mg/day)	Q4 (317.8–398.7 mg/day)	Q5 (>398.7 mg/day)	P value
Received college education or above	622 (48.3%)	698 (54%)	795 (61.5%)	817 (63.1%)	829 (64.4%)	***

*P<0.05. ***p<0.001.
†Any use of anti-inflammatory, antihyperlipidemic, antidepressant, antihypertensive or diuretic drug. Chi-squared test (categorical variables) and one-way analysis of variance (continuous variables) for subgroup differences.
E-alone, oestrogen-alone; E+P, oestrogen plus progestin; HRT, hormone replacement therapy; MCI, mild cognitive impairment; NS, not significant; PD, probable dementia; Q, quintile.

women developed MCI across the increasing quintiles of total Mg intake, whereas 395 (6.1%) women developed PD. When using the lowest quintile as the referent, the third quintile of total Mg intake was associated with the risk of composite MCI/PD (HR 0.69, 95% CI 0.53 to 0.91, p=0.01) in the fully adjusted model. Compared with the lowest quintile, the third (HR 0.63, 95% CI 0.45 to 0.87, p=0.01), fourth (HR 0.67, 95% CI 0.46 to 0.97, p=0.04) and fifth (HR 0.61, 95% CI 0.39 to 0.96, p=0.03) quintiles were associated with a lower risk of MCI in the fully adjusted model. None of the associations between Mg intake (both continuous or categorical variable) and the risk of PD were significant. The test for linear relationship was not significant in all fully adjusted models (model 2). For the association of total Mg intake with MCI/PD or MCI, adding the quadratic term of Mg intake to the regression model significantly improved the model fit, as shown by the likelihood ratio test (both p<0.01). This result indicated a non-linear relationship between the total Mg intake and cognitive decline. None of the models in table 2 violated the assumption of the Cox proportional hazards model.

Dietary Mg intake and risk of MCI/PD
Table 3 illustrates the association between dietary Mg intake and the risk of MCI and/or PD. None of the associations between the dietary Mg intake (both categorical variable and the test for trend) and the risk of MCI and/or PD were significant in the fully adjusted model (model 2). The test for linearity was not significant in all regression models and adding the quadratic term of Mg intake did not improve the model fit. None of the models in table 3 violated the assumption of the Cox proportional hazards model.

DISCUSSION
Summary of findings
We examined the association between the dietary Mg intake and cognitive impairment in a geographically diverse cohort of postmenopausal women in a WHI subcohort. When compared with the lowest quintile, the third quintile of total daily Mg intake (257.3–317.8 mg/day) was associated with a lower risk of composite MCI/PD and MCI after statistical adjustment for demographic

characteristics, diet, lifestyle, medication use and medical history. For MCI/PD and MCI, the HR estimates in models 1 and 2 were similar in magnitude. The reduced significance in model 2 possibly being due to the increased width of the 95% CI following statistical adjustment. No association was found between Mg intake and PD. Higher Mg intake may be associated with a lower risk of MCI but not necessarily in a dose-response manner. The association between the total Mg intake, MCI/PD and MCI were non-linear, as suggested by the likelihood test. The Mg intake from only the dietary source did not significantly associate with MCI/PD, possibly because the level of Mg intake from diet was lower than that from diet and supplementary sources combined.

Comparison with previous literature
Our findings are consistent with those of two previous studies that demonstrated the lowest risk cognitive decline among participants with a moderate Mg intake. Ozawa et al assessed the association between self-reported dietary intake of minerals (potassium, calcium and Mg) and dementia risk among older Japanese adults.[9] The HR for the development of all-cause dementia was 0.63 (95% CI 0.40 to 1.01) for the highest quartile (≥196 mg/day) of Mg intake compared with the lowest quartile (≤147 mg/day). For our study, the HR for the development of PD was also not significant (HR 1.25, 95% CI 0.75 to 2.08) for the highest quintile (>398.7 mg/day) of Mg intake compared with the lowest quintile (<197.4 mg/day). In another study from the Netherlands, a U-shaped distribution in the association between the Mg levels and cognition was observed such that both low (≤0.79 mmol/L) levels (HR 1.32) and high (≥0.90 mmol/L) serum Mg levels (HR 1.30) were associated with increased risk of all-cause dementia.[43] For our study, compared with the lowest quintile, the second quintile of total Mg intake was associated with the lowest risk of combined MCI/PD and MCI after adjusting for various confounders. The present findings support the total Mg intake (257.3–317.8 mg/day) between the estimated average requirement (estimated nutrient intake to meet the requirement of half of healthy individuals; 265 mg/day for women aged >51 years) and recommended dietary allowances (sufficient average daily dietary intake level to meet the nutrient

Table 2 Associations of total magnesium intake with the risk of mild cognitive impairment (MCI) and/or probable dementia (PD)

	Cases/Total	Model 1 (n=6473) HR (95% CI)†	P value	Model 2 (n=6183) HR (95% CI)†	P value
MCI/PD					
Total magnesium intake by quintiles					
Q1 (<197.4 mg/day)	184/1294	Ref		Ref	
Q2 (197.4–257.3 mg/day)	157/1295	0.82 (0.66 to 1.02)	NS	0.86 (0.68 to 1.08)	NS
Q3 (257.3–317.8 mg/day)	134/1295	0.65 (0.52 to 0.81)	***	0.69 (0.53 to 0.91)	*
Q4 (317.8–398.7 mg/day)	142/1295	0.73 (0.59 to 0.92)	*	0.77 (0.57 to 1.05)	NS
Q5 (>398.7 mg/day)	148/1294	0.73 (0.59 to 0.91)	*	0.81 (0.57 to 1.17)	NS
P value for trend					NS
P value for non-linearity					**
MCI					
Total magnesium intake by quintiles					
Q1 (<197.4 mg/day)	131/1294	Ref		Ref	
Q2 (197.4–257.3 mg/day)	106/1295	0.79 (0.61 to 1.02)	NS	0.77 (0.58 to 1.03)	NS
Q3 (257.3–317.8 mg/day)	87/1295	0.61 (0.47 to 0.81)	**	0.63 (0.45 to 0.87)	*
Q4 (317.8–398.7 mg/day)	91/1295	0.71 (0.54 to 0.93)	*	0.67 (0.46 to 0.97)	*
Q5 (>398.7 mg/day)	90/1294	0.66 (0.50 to 0.86)	**	0.61 (0.39 to 0.96)	*
P value for trend					NS
P value for non-linearity					**
PD					
Total magnesium intake by quintiles					
Q1 (<197.4 mg/day)	81/1294	Ref		Ref	
Q2 (197.4–257.3 mg/day)	77/1295	0.89 (0.65 to 1.22)	NS	1.02 (0.73 to 1.44)	NS
Q3 (257.3–317.8 mg/day)	72/1295	0.76 (0.55 to 1.05)	NS	0.87 (0.60 to 1.28)	NS
Q4 (317.8–398.7 mg/day)	80/1295	0.86 (0.63 to 1.18)	NS	1.06 (0.69 to 1.63)	NS
Q5 (>398.7 mg/day)	85/1294	0.92 (0.68 to 1.26)	NS	1.25 (0.75 to 2.08)	NS
P value for trend					NS
P value for non-linearity					NS

*P<0.05. **p<0.01, ***p<0.001.
†Model 1 adjustment: age at baseline, race/ethnicity, region in the USA, assignment of hormone therapy trial, BMI at baseline and smoking status.
‡Model 2 adjustment: covariates in model 1 along with education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B_6/B_9/B_{12}, total intake of calcium and vitamin D, dietary energy in kcal, baseline status of diabetes/cardiovascular disease/cancer, prior use of hormone replacement therapy, personal history of hypertension, personal history of high cholesterol requiring medications, family medical history of diabetes, family history of heart attack or stroke, use of anti-inflammatory drug, antihyperlipidaemia drug, antidepressant, antihypertensive drug or the use of diuretics at baseline.
BMI, body mass index; NS, not significant; Q, quintile.

requirement of 97%–98% healthy individuals; 320 mg/day for women aged >51 years) optimal for preventing cognitive decline.[44 45] Although further increment of Mg intake did not provide additional benefit for preventing MCI/PD, the fourth and fifth quintiles of total Mg intake associated with a lower MCI risk compared with the lowest quintile. Another observation is that total Mg intake had a similar magnitude of association with MCI/PD and MCI but is associated with the risk of PD without statistical significance. In other words, total Mg intake is more protective against MCI. Given that we assessed

the baseline diet only, the long follow-up period possibly weakened the association between the Mg intake and dementia.

Strengths and limitations
The strengths of the current analyses include the use of data from a large prospective cohort with long follow-up and the careful adjudication of MCI/PD events to ensure a high quality of outcome assessment. However, some limitations of assessment of Mg intake from dietary sources should be noted, for example, assessing the Mg

Table 3 Associations of dietary magnesium intake with the risk of mild cognitive impairment (MCI) and/or probable dementia (PD)

	Cases/Total	Model 1 (n=6473)		Model 2 (n=6183)	
		HR (95% CI)†	P value	HR (95% CI)‡	P value
MCI/PD					
Dietary magnesium intake by quintiles					
Q1 (<170.1 mg/day)	168/1294	Ref		Ref	
Q2 (170.1–216.1 mg/day)	160/1295	0.93 (0.75 to 1.16)	NS	0.96 (0.76 to 1.22)	NS
Q3 (216.1–263.2 mg/day)	144/1295	0.84 (0.67 to 1.05)	NS	0.86 (0.66 to 1.12)	NS
Q4 (263.2–323.3 mg/day)	144/1295	0.79 (0.63 to 0.99)	*	0.84 (0.63 to 1.13)	NS
Q5 (>323.3 mg/day)	149/1294	0.81 (0.65 to 1.01)	NS	0.86 (0.59 to 1.24)	NS
P value for trend					NS
P value for non-linearity					NS
MCI					
Dietary magnesium intake by quintiles					
Q1 (<170.1 mg/day)	118/1294	Ref		Ref	
Q2 (170.1–216.1 mg/day)	111/1295	0.95 (0.73 to 1.23)	NS	0.97 (0.73 to 1.29)	NS
Q3 (216.1–263.2 mg/day)	99/1295	0.87 (0.66 to 1.14)	NS	0.85 (0.62 to 1.17)	NS
Q4 (263.2–323.3 mg/day)	89/1295	0.76 (0.57 to 1.00)	NS	0.78 (0.55 to 1.13)	NS
Q5 (>323.3 mg/day)	88/1294	0.73 (0.55 to 0.97)	*	0.71 (0.45 to 1.14)	NS
P value for trend					NS
P value for non-linearity					NS
PD					
Dietary magnesium intake by quintiles					
Q1 (<170.1 mg/day)	76/1294	Ref		Ref	
Q2 (170.1–216.1 mg/day)	77/1295	0.95 (0.69 to 1.31)	NS	1.00 (0.70 to 1.42)	NS
Q3 (216.1–263.2 mg/day)	71/1295	0.86 (0.62 to 1.19)	NS	0.97 (0.66 to 1.41)	NS
Q4 (263.2–323.3 mg/day)	86/1295	0.97 (0.71 to 1.33)	NS	1.11 (0.74 to 1.67)	NS
Q5 (>323.3 mg/day)	85/1294	0.96 (0.70 to 1.31)	NS	1.08 (0.64 to 1.81)	NS
P value for trend					NS
P value for non-linearity					NS

*P<0.05.
†Model 1 adjustment: age at baseline, race/ethnicity, region in the USA, assignment of hormone therapy trial, BMI at baseline and smoking status.
‡Model 2 adjustment: covariates in model 1 along education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B_6/B_9/B_{12}, total intake of calcium and vitamin D, dietary energy in kcal, baseline status of diabetes/cardiovascular disease/cancer, prior use of hormone replacement therapy, personal history of hypertension, personal history of high cholesterol requiring medications, family medical history of diabetes, family history of heart attack or stroke, use of anti-inflammatory drug, antihyperlipidaemia drug, antidepressant, antihypertensive drug or the use of diuretics at baseline.
NS, not significant; Q, quintile.

intake at baseline only. The test based on the Schoenfeld residuals was not statistically significant. Therefore, the impact of Mg intake on MCI and/or PD was less likely to change over time. Moreover, we lack information on the serum Mg levels in the studied population. Despite the adjustment for dietary energy, assessment of dietary Mg intake can be confounded with other constituents, such as leafy green vegetables, which are the primary source of dietary Mg.[46] In addition, previous studies found that dietary Mg intake might not strongly correlate with serum Mg levels (r=0.28, p<0.05).[47] This condition may lead to

the different magnitudes of associations, including the impact of dietary/serum Mg on the risk of a disease, such as hypertension.[48] Moreover, supplemental Mg intake was collected for 'other supplement mixtures' and single supplements but not for standard multivitamins with minerals, the most common type of supplement used by WHI women. Although this limitation might lead to an under-ascertainment of Mg from supplements, whether this condition was the major flaw of this study is arguable because the total Mg intake demonstrated a significant association with MCI/PD. Furthermore, residual

confounding might occur due to inaccurate measurement of some adjustment variables, such as self-reported diet and physical activity. Last but not least, the present cohort included only postmenopausal women, and the findings may not be generalisable to elderly men. Despite these limitations, this study adds important information regarding Mg intake for cognitive benefit in postmenopausal women.

CONCLUSIONS

Among postmenopausal women from WHIMS with over 20 years of follow-up, the total Mg intake between the estimated average requirement and recommended dietary Allowances was associated with a low risk of composite MCI/PD and MCI but not in a dose-response manner.

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