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Relations of Magnesium Intake to Cognitive Impairment and Dementia Among Women participated in Women's Health Initiative Memory Study

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Abstract

Objective: To examine the associations of dietary and supplemental magnesium (Mg) with cognitive outcomes in aging women.

Design, setting and participants: We analyzed data from Women's Health Initiative Memory Study (WHIMS) and Women's Health Initiative Memory Study-Epidemiology of Cognitive Health (WHIMS-ECHO), which involved 7,479 postmenopausal women aged 65 to 79 with cognitive decline at enrollment.

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

Results: Among postmenopausal women from WHIMS and WHIMS-ECHO with over 20 years of follow-up, 6,473 of them were included in the analysis after excluding women who had extreme values of dietary energy intake, had missing or extreme BMI values, with prevalent MCI/PD at baseline, received only one cognitive assessment, or had been followed-up for less than one year. A total of 765 participants (11.8%) developed MCI or PD. When compared with the lowest tertile, the second tertile of total Mg intake was significantly associated with 33% lower adjusted risk of combined MCI/PD (HR = 0.67, 95% C.I. = 0.51, 0.88, p<0.01) and 35% lower risk of MCI (HR = 0.65, 95% C.I. = 0.47, 0.88, p=0.01) in fully adjusted model (adjusted for demographic characteristics, diet, lifestyle, medication use and medical history). The third terile did not appear to have significant protective effect against MCI or PD.

Conclusions: Total Mg intake between Estimated Average Requirement and Recommended Dietary Allowances may be associated with lower risk of composite MCI/PD and MCI, while further increment of Mg intake did not provide additional benefit. Higher Mg intake from diet should be an effective strategy in preventing cognitive decline.

Trial registration: clinicaltrials.gov (NCT00685009)

Article focus

- To examine the associations of dietary and supplemental magnesium (Mg) with cognitive outcomes in aging women.

Key messages

- Total Mg intake between Estimated Average Requirement and Recommended Dietary Allowances may be associated with lower risk of cognitive decline, while further increment of Mg intake did not provide additional benefit.

Strengths and limitations of this study

- A large prospective cohort with long follow-up, and careful adjudication of MCI/PD events to ensure a high quality of outcome assessment.
- Lacking information on serum Mg levels in the studied population.
- The present cohort included only postmenopausal women, and the findings may not be generalizable to elder men.

Background

Mild cognitive impairment (MCI) involves onset and evolution of cognitive impairments beyond those expected based on an individual's age and education but not significant enough to interfere with her or his daily activities.[1] Cognitive function might decline progressive over time for people with MCI, which impaired their memory, reasoning, language and visuospatial abilities. Individuals are diagnosed with dementia when their cognitive decline has interfered with daily function.[2] Dementia affects approximately 47 million people worldwide, and its prevalence is expected to more than triple by 2050.[3] The prevalence of dementia and associated medical costs have increased dramatically in recent years in parallel with the aging population globally, which has increased the healthcare burden to communities, families and individuals.[3] Compared to older men, older women have higher lifetime risk for dementia[4, 5] and faster progression of cognitive impairment following

diagnosis.[6] Therefore, identifying 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 of to prevent vascular outcomes. Recent work has shown that magnesium may regulate N-methyl-D-aspartate (NMDA) receptors, which affect critical functions of the central nervous system including neuronal development, plasticity and neurodegeneration. NMDA receptor is permeable to calcium, sodium and potassium ions and can be blocked by Mg ions.[7] While strong neurobiological data are in support of the role of Mg intake for normal neuron functioning by helping to prevent the destruction of neurons resulting from NMDA-induced excitotoxicity[8], few prospective studies have directly examined the relation between Mg intake (dietary and/or supplements) and risk of dementia.[9, 10] We therefore conducted a prospective investigation of the role of Mg intake in the development of two constructs of cognitive decline, namely mild cognitive impairment (MCI) and probable dementia (PD) among older women who participated in the Women's Health Initiative Memory Study (WHIMS; 1995-2008) and were followed in the WHIMS-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO; 2008-onwards) Study.

Methods

Data source

WHI Memory Study (WHIMS)is an ancillary study to the WHI Hormone Trial (N=27,347 for the whole trial) that was designed to assess the effect of postmenopausal hormone therapy (HT) on dementia risk.[11] Invitation to participate was sent to WHI Hormone Therapy Trial women that aged 65 to 79 years without dementia at enrollment.[12] Following termination of the HT intervention, in WHIMS (1995-2008, 7,479 participants) and subsequent WHIMS-ECHO follow-up (2008 onwards, ~2900 participants), there were continued annual

assessments of cognitive function and adjudication of all-cause dementia and MCI status.

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 extreme values of dietary energy intake (<600 kcal or >5000 kcal), had missing or extreme BMI values (BMI<15 kg/m^2 or BMI>50 kg/m^2), women with prevalent MCI/PD at baseline and received only one Modified Mini- Mental State Examination (3MSE) for cognitive assessment. Lastly, to avoid reverse causation between dietary intake and disease onset, we only included women who had been followed-up for at least one year. Details of participant selection are illustrated in **Figure 1**.

Outcome Variable

The WHIMS and WHIMS-ECHO protocol used a multi-phase approach to identify cases of MCI and PD. From 1995 through 2007 (WHIMS), participants were screened annually in clinic by trained and certified examiners with the Modified Mini- Mental State Examination (3MSE). The 3MSE ranges from 0 to 100, and initial cut-points for further testing are 72 or lower for participants with <9 years of education, and 76 or lower for participants with 9 years or more of education. After July 1, 1998 the cut points were 80 and 88 respectively. Participants who scored below the education-adjusted 3MSE cut-point received the in-depth multi-phased evaluation,[13] including a battery of neuropsychologic tests, history and physical, neuropsychiatric evaluation, and an interview of friend or family member to assess functional status[11].

Beginning in 2008 (WHIMS-ECHO), an annual validated cognitive test battery that included the Telephone Interview for Cognitive Status-modified (TICSm)[14] and other validated tests of cognitive function were administered by telephone. [15] To justify replacing 3MSE assessment

with TICSm, a validation study was conducted. Results showed that the 3MSE scores predicted by TICSm was highly correlated (0.82) with 3MSE scores,[16] while the transformation of WHIMS 3MSE and WHIMS-ECHO TICSm data into relative percentile ranks fit the trajectories of global cognitive function.[17] For women who screened positive (i.e., TICSm<31) during WHIMS-ECHO follow-up, a reliable and pre-identified informant was interviewed by telephone using the standardized Dementia Questionnaire to assess the history of cognitive and behavioral 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 center. The committee had experts experienced in neurological examinations and neuropsychiatric evaluations, where cases are classified as no impairment, MCI or PD. [19] Outcome classification was based on the DSM-IV criteria for dementia [20] and Petersen's MCI criteria[1] .

Exposure variable

Dietary Mg intake at baseline was derived using the baseline WHI semi-quantitative food frequency questionnaire (FFQ).[21] The nutrient database for the WHI FFQ uses the Nutrition Data Systems for Research (NDS-R, version 2005, University of Minnesota Nutrition Coordinating Center, Minneapolis, MN) food and nutrient database.[22] Data on 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, which has demonstrated high correlation (ranged from 0.8 to 1.0) with photo-copied labels in validation study.[24] Total Mg intake was calculated by summation of dietary and supplemental Mg intake. To test the linear relationship between total Mg intake and

MCI/PD, levels of Mg intake were categorized per 100mg increments or categorized into tertiles.

Covariates

At WHI baseline, WHIMS participants completed questionnaires on various information, including demographics (age, race-ethnicity), socioeconomic status (education in years), lifestyle factors (diet, smoking, alcohol use, 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, anti-hyperlipidemia drugs, anti-depressants, anti-hypertensive drugs or diuretics). Height and weight were measured at baseline for calculating Body Mass Index (BMI).

Data analysis

Descriptive statistics were demonstrated by tertiles of total magnesium intake. In order to preserve statistical power with regard to the sample size, tertile was chosen instead of quartile or quintile in the present study. The differences between tertiles were tested by one-way ANOVA for continuous variables and chi-square 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 hazard ratios (HRs) and associated 95% confidence intervals (95% CI). 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 end-point of MCI/PD was presented as a combined end-point in primary analyses. MCI and PD were treated as secondary end-points respectively. The event time was defined as the time of screening by global cognitive tests (either 3MS or TICSm) that triggered the subsequent work-up that

concluded with the central adjudication of first MCI/PD. If a participant had progressed from MCI to PD, she was classified as a case of PD instead of MCI. To test the assumption of Cox proportional hazards model, i.e. whether the predictive ability of independent variables changed with time, we calculated interactions of predictor variables and the survival time (time to event or the end of follow-up) and included the interaction term in the models. A sensitivity analysis was performed by using dietary or supplementary Mg intake only and was categorized in tertiles and per 100mg increments.

To ensure robustness of regression analysis, we have controlled for confounders with reference to previous studies of cognitive decline. Model 1 was the minimally adjusted model and included age at baseline, region in U.S., race/ethnicity, assignment arm of HT trial, BMI at baseline[28] and smoking status.[29] Model 2 included covariates in Model 1 plus education,[30] dietary variables and physical activity (alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, total intake of calcium and vitamin D),[27, 31-34] as well as 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 (includes cardiac arrest, congestive heart failure, cardiac catheterization, coronary bypass surgery, angioplasty of coronary arteries, carotid endarterectomy/angioplasty, atrial fibrillation or aortic aneurysm)[36] and 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, medication use (anti-inflammatory drugs, anti-hyperlipidemia drugs, anti-depressants, anti-hypertensive 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 3.5.1. P values less than 0.05 were considered statistically significant.

Patient and public involvement

No patients were involved in the design process of this study, setting 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 6,473 participants were included in the analyses. The baseline characteristics of participants in the WHIMS by tertiles are presented in **Table 1**. Women in the highest tertile of Mg intake tended to have, on average, lower BMI, greater energy expenditure from recreational physical activity and higher levels of all dietary variables as shown by one-way ANOVA. As demonstrated by chi-square test, Non-Hispanic White women, participants enrolled in controlled group of Estrogen+Progestin trial, participants with ≥7 alcohol drinks per week, being a past smoker or receiving post-college education were more prevalent to have the highest level of Mg intake.

Total Magnesium intake and risk of Mild Cognitive Impairment/Probable Dementia

Table 2 illustrates the association between total Mg intake and risk of MCI and/or PD. A total of 208 (9.6%), 142 (6.5%) and 155 (7.2%) women developed MCI across the increasing tertiles of total Mg intake, while 133 (6.2%), 118 (5.4%) and 144 (6.7%) women developed PD. Total Mg intake per 100mg increment was not associated with risk of MCI and/or PD in any of the Cox models assuming a linear association. When using the lowest tertile as the referent, the second tertile of total Mg intake was associated with risk of composite MCI/PD (HR = 0.65, 95% C.I. = 0.51, 0.88, $p<0.01$) and MCI (HR = 0.65, 95% C.I. = 0.47, 0.88,

p=0.01) in fully adjusted model. None of the associations between Mg intake (both continuous or categorical variable) and the risk of PD were significant. After full adjustments, interactions between most predictor variables and survival time were not significant (p value ranged from 0.05 to 0.45), so the proportional hazard assumption was not violated (**Table 2**). The only exception was the null association between total magnesium intake per 100mg increment and the risk of MCI (p value for interaction with time=0.03).

Dietary Magnesium intake and risk of Mild Cognitive Impairment/Probable Dementia

Table 3 illustrates the association between dietary Mg intake and risk of MCI and/or PD. A total of 190 (8.8%), 169 (7.8%) and 146 (6.8%) women developed MCI across the increasing tertiles of dietary Mg intake, while 132 (6.1%), 119 (5.5%) and 144 (6.7%) women developed PD. None of the associations between dietary Mg intake (both continuous or categorical variable) and the risk of MCI and/or PD were significant in the fully adjusted model (Model 2). After full adjustments, interactions between predictor variables and survival time were not significant (p value ranged from 0.29 to 0.58), so the proportional hazard assumption was not violated (**Table 3**).

Discussion

Summary of findings

We examined the association between dietary Mg intake and cognitive impairment in a geographically-diverse cohort of post-menopausal women in a sub-cohort of the WHI. When compared with the lowest tertile, the second tertile of total daily Mg intake was associated with lower risk of composite MCI/PD and MCI after statistical adjustment for demographic characteristics, diet, lifestyle, medication use and medical history. No association was found between Mg intake and PD. Higher Mg intake may be associated with lower risk of mild cognitive impairment, but not necessarily in a dose-response manner. Although Mg intake

from dietary source only did were not significantly associate with MCI/PD, the results appeared to be intuitive because the levels of Mg intake from dietary source was lower than the sum of dietary and supplemental source. Although the association between total magnesium intake per 100mg increment and the risk of MCI violated the assumption of Cox regression, this result did not alter the interpretation of overall findings.

Comparison with previous literature

Our findings were consistent with two previous studies that demonstrated the lowest risk cognitive decline among participants with moderate Mg intake. Ozawa and colleagues assessed the association between self-reported dietary intake of minerals (potassium, calcium, and magnesium) and dementia risk among Japanese older adults.[9] The hazard ratio for the development of all-cause dementia was 0.63 (95% CI = 0.40–1.01) for the highest quartile (≥196 mg/d) of Mg intake compared to the lowest quartile (≤147 mg/d). For our study, the hazard ratio for the development of probable dementia was also insignificant (HR: 1.05, 95% CI = 0.48–2.29) for the highest tertile (>337.6mg/d) of Mg intake compared to the lowest tertile (<236.9mg/d). In another study from the Netherlands, a "U" shaped distribution in the association between 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, comparing with the lowest tertile, the second tertile of total Mg intake was associated with lowest risk of combined MCI/PD and MCI after adjusting for various confounders. The present findings do support total Mg intake (238.6-341.2mg) between Estimated Average Requirement (estimated nutrient intake to meet the requirement of half the healthy individuals, 265mg/day for women >51 years old) and Recommended Dietary Allowances (sufficient average daily dietary intake level to meet the nutrient requirement of 97 to 98% healthy individuals, 320mg/day for women >51 years old) is optimal for preventing cognitive decline,[44, 45] while

further increment of Mg intake did not provide additional benefit. Another observation is that total Mg intake had similar magnitude of association with MCI/PD and MCI but associated with the risk of PD without statistical significance. In other words, total Mg intake is more protective against MCI. Since we only assessed baseline diet, it is possible that long follow-up period weakened the association between Mg intake and dementia.

Strengths and Limitations

Strengths of the current analyses include the use of data from a large prospective cohort with long follow-up, and 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. We are lacking information on serum Mg levels in the studied population. Despite adjustment for dietary energy, assessment of dietary Mg intake can be confounded with other constituents such as leafy green vegetables, the primary source of dietary Mg.[46] In addition, previous studies have found that dietary Mg intake might not strongly correlate with serum Mg levels ($r=0.28$, $p<0.05$).[47] That may lead to different magnitudes of associations, such as the impact of dietary/serum Mg on the risk of a disease, such as described for hypertension.[48] Moreover, supplemental Mg intake was collected for 'other supplement mixtures' and single supplements but not for standard multivitamins with minerals which was the most common type of supplement used by WHI women. Although this limitation might lead to under-ascertainment of Mg from supplements, whether it was the major flaw of this study was arguable, since the total Mg intake has demonstrated significant association with MCI/PD. Last but not least, the present cohort included only postmenopausal women, and the findings may not be generalizable to elder 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, total Mg intake between Estimated Average Requirement and Recommended Dietary Allowances was associated with lower risk of composite MCI/PD and MCI despite not in a dose-response manner.

Contributors: KL, QL, TM, AHS, LP, XL, SS, JEM searched the literature; analyzed and interpreted the data; and wrote the manuscript. SR, JCC, MN, SL participated in the study design; collected, analyzed, and interpreted the data; and wrote the manuscript.

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Ethics approval: The WHI study was approved by the research ethics committees at each of the participating centers.

Competing interests: None declared.

Data sharing: No additional data available.

Provenance and peer review: Not commissioned; externally peer reviewed.

Figure 1 Identification of an Analytical Cohort from the Women's Health Initiative Memory Study (WHI-MS)

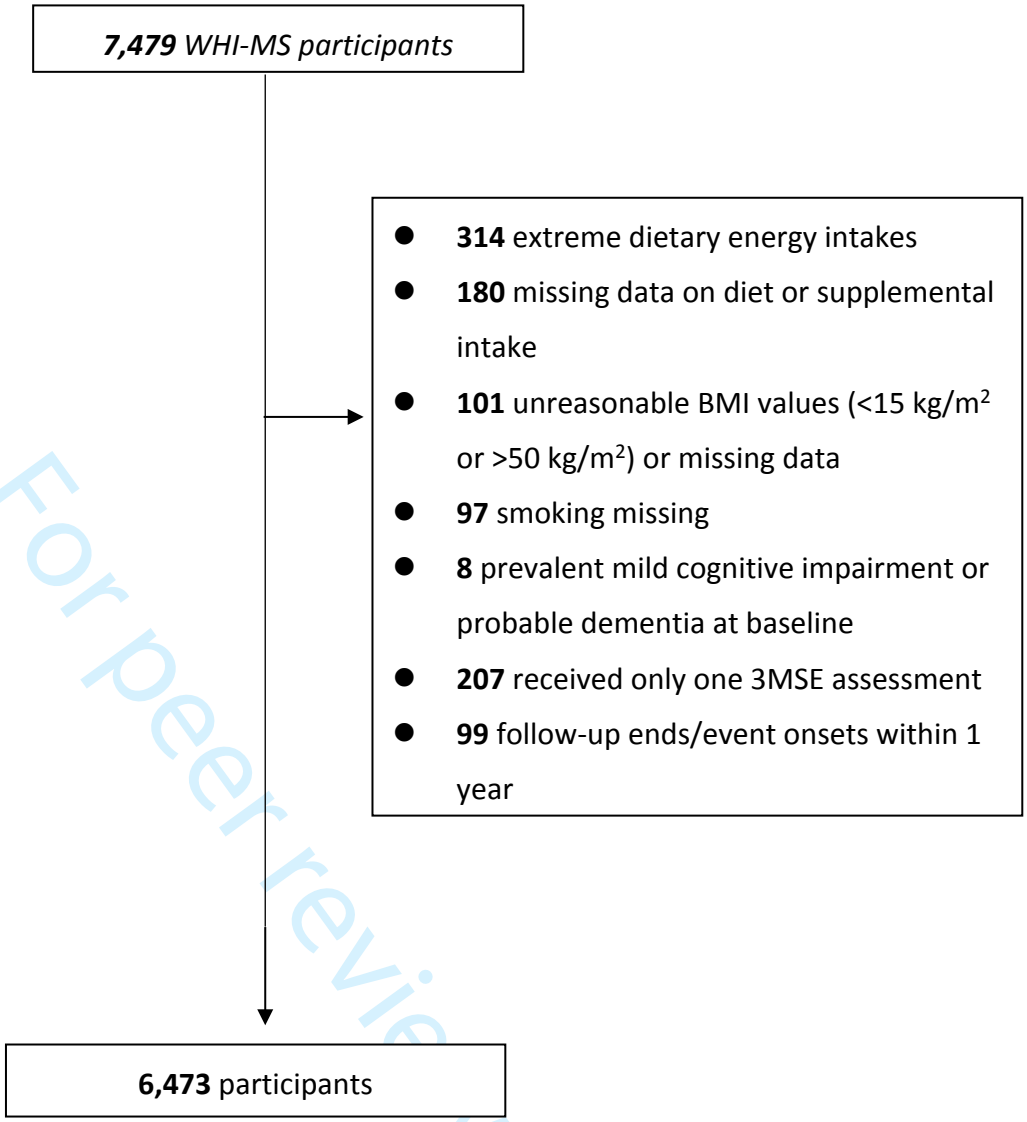

Table 1 Baseline Characteristics of Participants in The Women's Health Initiative Memory Study by tertiles of Total Mg Intake

	Mean (SD) / N (%)			
	T1	T2	T3	p value
Time-to-event/censored	9.2 (4.4)	9.8 (4.3)	9.8 (4.3)	<0.01*
Age at baseline in years	70.0 (3.7)	70.1 (3.9)	70.2 (3.9)	0.37
BMI at baseline	28.6 (5.3)	28.2 (5.4)	28.3 (5.4)	0.04*
Recreational physical activity in MET-hour	9.8 (12.4)	11.1 (12.6)	13.0 (14.3)	<0.01*
Total B6 intake in mg	4.1 (19.9)	5.8 (21.5)	10.6 (39.2)	<0.01*
Total B9 intake in mcg	265.5 (200.0)	455.1 (203.0)	652.1 (261.6)	<0.01*
Total B12 intake in mcg	15.1 (75.4)	17.0 (55.0)	29.3 (84.6)	<0.01*
Total calcium intake in mg	717.0 (578.3)	1100.7 (545.9)	1599.8 (663.9)	<0.01*
Total vitamin D intake in mcg	4.8 (4.3)	9.4 (5.4)	14.2 (6.6)	<0.01*
Dietary energy in kcal	1183.0 (350.2)	1595.6 (451.8)	2036.6 (694.1)	<0.01*
Region in U.S.				0.56
● Northeast	597 (27.7%)	596 (27.6%)	578 (26.8%)	
● South	461 (21.4%)	430 (19.9%)	424 (19.6%)	
● Midwest	506 (23.5%)	533 (24.7%)	559 (25.9%)	
● West	593 (27.5%)	599 (27.8%)	597 (27.7%)	
Race/Ethnicity				<0.01*
● Non-Hispanic White	1782 (82.6%)	1940 (89.9%)	1961 (90.9%)	
● Black or African-American	208 (9.6%)	108 (5.0%)	99 (4.6%)	
● Hispanic/Latino	77 (3.6%)	35 (1.6%)	32 (1.5%)	
● Other	86 (4.0%)	72 (3.3%)	59 (2.7%)	
HRT Arm				<0.01*
● E-alone	495 (22.9%)	387 (17.9%)	366 (17.0%)	
● E-alone control	443 (20.5%)	385 (17.8%)	429 (19.9%)	
● E+P intervention	603 (28.0%)	692 (32.1%)	640 (29.7%)	
● E+P control	616 (28.6%)	694 (32.2%)	723 (33.5%)	
7+ alcohol drinks per week	219 (10.2%)	264 (12.2%)	327 (15.2%)	<0.01*
Prevalent diabetes	184 (8.5%)	160 (7.4%)	163 (7.6%)	0.32
Prevalent cardiovascular disease	355 (16.5%)	351 (16.3%)	377 (17.5%)	0.56
Prevalent cancer	88 (4.1%)	72 (3.3%)	72 (3.3%)	0.32
Hormone Replacement Therapy				0.15
● Never used	1482 (68.7%)	1495 (69.3%)	1467 (68.0%)	
● Past user	571 (26.5%)	529 (24.5%)	557 (25.8%)	
● Current user	104 (4.8%)	134 (6.2%)	134 (6.2%)	
Treated high cholesterol	391 (18.1%)	370 (17.1%)	390 (18.1%)	0.61

History of hypertension	856 (39.7%)	831 (38.5%)	805 (37.3%)	0.27
Family history of diabetes, heart attack or stroke	1662 (77.1%)	1689 (78.3%)	1640 (76.0%)	0.21
Medication use [a]	1007 (46.7%)	986 (45.7%)	1016 (47.1%)	0.64
Smoking status				<0.01*
● Never Smoked	1134 (52.6%)	1168 (54.1%)	1144 (53.0%)	
● Past Smoker	838 (38.9%)	845 (39.2%)	914 (42.4%)	
● Current Smoker	185 (8.6%)	145 (6.7%)	100 (4.6%)	
Received college education or above	1070 (49.6%)	1312 (60.8%)	1379 (63.9%)	<0.01*

MCI: mild cognitive impairment; PD: probable dementia; HRT: Hormone replacement therapy; E-alone: Estrogen-alone:E+P:Estrogen+Progestin

* *P* value < 0.05

[a] Any use of anti-inflammatory, anti-hyperlipidemic, anti-depressant, anti-hypertensive or diuretic drug

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

	Cases/Total	Model 1 (95% C.I.) [a]	p value	Model 2 (95% C.I.) [b]	p value
		N=6,473		N=6,183	
MCI/PD					
Total magnesium intake (per 100mg increment)		0.86 (0.77, 0.97)	0.02*	0.95 (0.84, 1.08)	0.43
Total magnesium intake by tertiles					
● T1 (<238.6 mg/day)	295/2157	Ref		Ref	
● T2 (238.6-341.2 mg/day)	222/2158	0.61 (0.48, 0.78)	<0.01*	0.67 (0.51, 0.88)	<0.01*
● T3 (>341.2 mg/day)	248/2158	0.60 (0.41, 0.88)	0.01*	0.72 (0.46, 1.12)	0.14
Mild Cognitive Impairment					
Total magnesium intake (per 100mg increment)		0.82 (0.72, 0.94)	<0.01*	0.86 (0.74, 1.00)	0.05
Total magnesium intake by tertiles					
● T1 (<238.6 mg/day)	208/2157	Ref		Ref	
● T2 (238.6-341.2 mg/day)	142/2158	0.59 (0.45, 0.77)	<0.01*	0.65 (0.47, 0.88)	0.01*
● T3 (>341.2 mg/day)	155/2158	0.55 (0.36, 0.84)	0.01*	0.63 (0.38, 1.04)	0.07
Probable dementia					
Total magnesium intake (per 100mg increment)		1.00 (0.86, 1.17)	0.98	1.04 (0.89, 1.21)	0.66
Total magnesium intake by tertiles					
● T1 (<238.6 mg/day)	133/2157	Ref		Ref	
● T2 (238.6-341.2 mg/day)	118/2158	0.81 (0.56, 1.17)	0.26	0.86 (0.58, 1.28)	0.46
● T3 (>341.2 mg/day)	144/2158	0.93 (0.51, 1.68)	0.80	1.10 (0.56, 2.16)	0.78

[a] Model adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status.

[b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline *P<0.05.

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

	Cases/Total	Model 1 (95% C.I.) [a]	p value	Model 2 (95% C.I.) [b]	p value
		N=6,473		N=6,183	
MCI/PD					
Dietary magnesium intake (per 100mg increment)		0.89 (0.75, 1.06)	0.19	0.92 (0.75, 1.14)	0.45
Dietary magnesium intake by tertiles					
● T1 (<203.0mg/day)	276/2157	Ref		Ref	
● T2 (203.0-280.6mg/day)	242/2158	0.77 (0.60, 0.98)	0.03*	0.82 (0.63, 1.07)	0.14
● T3 (>280.6mg/day)	247/2158	0.70 (0.47, 1.03)	0.07	0.79 (0.50, 1.24)	0.31
Mild Cognitive Impairment					
Dietary magnesium intake (per 100mg increment)		0.85 (0.71, 1.03)	0.09	0.87 (0.69, 1.10)	0.25
Dietary magnesium intake by tertiles					
● T1 (<203.0mg/day)	190/2157	Ref		Ref	
● T2 (203.0-280.6mg/day)	169/2158	0.81 (0.61, 1.06)	0.13	0.87 (0.64, 1.18)	0.36
● T3 (>280.6mg/day)	146/2158	0.62 (0.40, 0.96)	0.03	0.73 (0.44, 1.23)	0.24
Probable dementia					
Dietary magnesium intake (per 100mg increment)		1.04 (0.81, 1.34)	0.75	1.05 (0.78, 1.42)	0.73
Dietary magnesium intake by tertiles					
● T1 (<203.0mg/day)	132/2157	Ref		Ref	
● T2 (203.0-280.6mg/day)	119/2158	0.86 (0.60, 1.24)	0.42	0.93 (0.62, 1.38)	0.70
● T3 (>280.6mg/day)	144/2158	1.01 (0.56, 1.83)	0.98	1.06 (0.54, 2.09)	0.86

[a] Model adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status. [b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline *P<0.05.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	15
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	17-18

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	17-18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

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

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Abstract

Objective: Dietary and supplemental magnesium (Mg) as assessed by food frequency questionnaire at baseline to examine their associations with cognitive outcomes in aging women.

Design, setting and participants: We analyzed data from postmenopausal women that enrolled in Women's Health Initiative Memory Study (WHIMS). WHIMS was subsequently extended and named WHIMS-Epidemiology of Cognitive Health (WHIMS-ECHO). WHIMS-ECHO involved the same group participants that remained in the cohort.

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

Results: After excluding women who had extreme values of dietary energy intake, had missing or extreme BMI values, with prevalent MCI/PD at baseline, received only one cognitive assessment, or had been followed-up for less than one year, we included 6,473 of them in the analysis. With over 20 years of follow-up, 765 participants (11.8%) developed MCI or PD. When compared with the lowest quintile, the third quintile of total Mg intake was significantly associated with a 33% lower adjusted risk of combined MCI/PD (HR = 0.69, 95% CI = 0.53, 0.91, p=0.01) and MCI (HR = 0.63, 95% CI = 0.45, 0.87, p=0.01) after adjustment for every conceivable variable (demographic characteristics, diet, lifestyle, medication use and medical history).

Conclusions: Total Mg intake between the Estimated Average Requirement and the Recommended Dietary Allowances may be associated with a lower risk of composite MCI/PD and MCI. Further increment of Mg intake did not provide additional benefit. Higher Mg intake from diet should be an effective strategy in preventing cognitive decline.

Trial registration: clinicaltrials.gov (NCT00685009)

Strengths and limitations of this study

- A large prospective cohort with long follow-up, and careful adjudication of MCI/PD events to ensure a high quality of outcome assessment.
- Lacking information on serum Mg levels in the studied population.
- The present cohort included only postmenopausal women, and the findings may not be generalizable to elder men.

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 enough to interfere with her or his daily activities.[1] Cognitive function might decline progressively over time for people with MCI, which impaired their memory, reasoning, language and visuospatial abilities. Individuals are diagnosed with dementia when their cognitive decline has interfered with daily function.[2] Dementia affects approximately 47 million people worldwide, and its prevalence is expected to more than triple by 2050.[3] The prevalence of dementia and associated medical costs have increased dramatically in recent years in parallel with the aging population globally, which has increased the healthcare burden to communities, families and individuals.[3] Compared to older men, older 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 of to prevent vascular outcomes. Recent work has shown that magnesium may regulate N-methyl-D-aspartate (NMDA)

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

Methods

Data source

The WHI Memory Study (WHIMS) is an ancillary study to the WHI Hormone Trial (N=27,347 for the whole trial) that was designed to assess the effect of postmenopausal hormone therapy (HT) on dementia risk.[11] Invitation to participate was sent to WHI Hormone Therapy Trial women that aged 65 to 79 years without dementia at enrollment.[12] Following termination of the HT intervention, in WHIMS (1995-2008, 7,479 participants) and subsequent WHIMS-ECHO follow-up (2008 onwards, ~2900 participants), there were continued annual assessments of cognitive function and adjudication of all-cause dementia and MCI status. The ethical approval of all protocols were obtained from the institutional review boards (IRBs) of all participating institutions (40 clinical site IRBs, the coordinating center IRB and

ethical review at National Institutes of Health). Written informed consent was obtained from participants.

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 extreme values of dietary energy intake (<600 kcal or >5000 kcal), had missing or extreme BMI values (BMI<15 kg/m^2 or BMI>50 kg/m^2), women with prevalent MCI/PD at baseline and received only one Modified Mini- Mental State Examination (3MSE) for cognitive assessment. Lastly, to avoid reverse causation between dietary intake and disease onset, we only included women who had been followed-up for at least one year. The details of participant selection are illustrated in **Supplementary Figure 1**.

Outcome Variable

The WHIMS and WHIMS-ECHO protocol used a multi-phase approach to identify cases of MCI and PD. From 1995 through 2007 (WHIMS), participants were screened annually in clinic by trained and certified examiners with the Modified Mini- Mental State Examination (3MSE). The 3MSE ranges from 0 to 100, and initial cut-points for further testing are 72 or lower for participants with <9 years of education, and 76 or lower for participants with 9 years or more of education. After 1st July 1998, the cut points were 80 and 88 respectively. Participants who scored below the education-adjusted 3MSE cut-point received the in-depth multi-phased evaluation,[13] including a battery of neuropsychologic tests, history and physical, neuropsychiatric evaluation, and an interview of friend or family member to assess functional status[11].

Beginning in 2008 (WHIMS-ECHO), an annual validated cognitive test battery that

included the Telephone Interview for Cognitive Status-modified (TICSm)[14] and other validated tests of cognitive function were administered by telephone. [15] To justify replacing 3MSE assessment with TICSm, a validation study was conducted. Results showed that the 3MSE scores predicted by TICSm was highly correlated (0.82) with 3MSE scores,[16] while the transformation of WHIMS 3MSE and WHIMS-ECHO TICSm data into relative percentile ranks fit the trajectories of global cognitive function.[17] For women who were screened positive (i.e., TICSm<31) during WHIMS-ECHO follow-up, a reliable and pre-identified informant was interviewed by telephone using the standardized Dementia Questionnaire to assess the history of cognitive and behavioral 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 center. The committee had experts experienced in neurological examinations and neuropsychiatric evaluations, where cases are classified as no impairment, MCI or PD. [19] Outcome classification was based on the DSM-IV 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 food frequency questionnaire (FFQ).[21] The nutrient database for the WHI FFQ uses the Nutrition Data Systems for Research (NDS-R, version 2005, University of Minnesota Nutrition Coordinating Center, Minneapolis, MN) food and nutrient database.[22] The data on 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, which has demonstrated high correlation (ranged from 0.8 to 1.0) with photo-copied labels in 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, levels of Mg intake were categorized into quintiles.

Covariates

At WHI baseline, WHIMS participants completed questionnaires on various information, including demographics (age, race-ethnicity), socioeconomic status (education in years), lifestyle factors (diet, smoking, alcohol use, 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, anti-hyperlipidemia drugs, anti-depressants, anti-hypertensive drugs or diuretics). Height and weight were measured at baseline for calculating Body Mass Index (BMI).

Data analysis

Descriptive statistics were demonstrated by the quintiles of total magnesium intake. The differences between quintiles were tested by one-way ANOVA for continuous variables and chi-square 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 hazard ratios (HRs) and associated 95% confidence intervals (95% CI). 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 end-point of MCI/PD was presented as a combined end-point in primary analyses. MCI and PD were treated as secondary end-points respectively. The event time was defined as the time of screening by global cognitive tests (either 3MS or TICSm) that triggered the subsequent work-up that concluded with the central adjudication of first MCI/PD. If a participant had progressed from MCI to PD, she was classified as a case of PD instead of MCI. The test for linear relationship by conducted by assigning median values for quintiles, then treated it as a continuous variable in regression model. To examine potential non-linear relationship between 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, hence non-linear relationship between Mg intake and cognitive outcomes. To test the assumption of Cox proportional hazards model, we examined all models using the Schoenfeld residual test. A sensitivity analysis was performed by using dietary Mg intake only.

To ensure robustness of regression analysis, we have controlled for confounders with reference to previous studies of cognitive decline. Model 1 was the minimally adjusted model and included age at baseline, region in U.S., race/ethnicity, assignment arm of HT trial, BMI at baseline[28] and smoking status.[29] Model 2 included covariates in Model 1 plus education,[30] dietary variables and physical activity (alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, total intake of calcium and vitamin D),[27, 31-34] as well as 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 (includes cardiac arrest, congestive heart failure, cardiac catheterization, coronary bypass surgery, angioplasty of coronary arteries, carotid endarterectomy/angioplasty, atrial fibrillation or aortic aneurysm)[36] and 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, medication use (anti-inflammatory drugs, anti-hyperlipidemia drugs, anti-depressants, anti-hypertensive 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 3.6.0. P values less than 0.05 were considered statistically significant.

Patient and public involvement

No patients were involved in the design process of this study, setting 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 6,473 participants were included in the analyses. The baseline characteristics of participants in the WHIMS by quintiles are presented in **Table 1**. Women in the highest quintiles of Mg intake tended to have, on average, 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 chi-square test, Non-Hispanic White women, participants enrolled in

controlled group of Estrogen+Progestin trial, participants with ≥7 alcohol drinks per week, having a history of cardiovascular disease or hypertension, being a past smoker or receiving post-college education were more prevalent to have the highest level of Mg intake. The baseline characteristics of participants included (N=6473) or excluded (N=1006) from the analysis was compared in **Supplementary Table 1**. Between-group difference was significant for majority of variables except for the baseline age, recreational physical activity, total B6 and B12 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 Mild Cognitive Impairment/Probable Dementia

Table 2 illustrates the association between total Mg intake and risk of MCI and/or PD. A total of 505 (7.8%) women developed MCI across the increasing quintiles of total Mg intake, while 395 (6.1%) women developed PD. When using the lowest quintile as the referent, the third quintile of total Mg intake was associated with risk of composite MCI/PD (HR = 0.69, 95% CI = 0.53, 0.91, p=0.01) in the fully adjusted model. Comparing with the lowest quintile, the third (HR = 0.63, 95% CI = 0.45, 0.87, p=0.01), fourth (HR = 0.67, 95% CI = 0.46, 0.97, p=0.04) and fifth (HR = 0.61, 95% CI = 0.39, 0.96, p=0.03) quintile associated with 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 insignificant 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 into the regression model significantly improved the model fit as shown by the likelihood ratio test (both p=0.01), which indicated a non-linear relationship between total Mg intake and cognitive decline. None of the models in Table 2 violated the

assumption of Cox proportional hazards model.

Dietary Magnesium intake and risk of Mild Cognitive Impairment/Probable Dementia

Table 3 illustrates the association between dietary Mg intake and risk of MCI and/or PD. None of the associations between 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 insignificant in all regression models, while adding the quadratic term of Mg intake did not improve the model fit. None of the models in Table 3 violated the assumption of Cox proportional hazards model.

Discussion

Summary of findings

We examined the association between dietary Mg intake and cognitive impairment in a geographically diverse cohort of post-menopausal women in a sub-cohort of the WHI. 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 the statistical adjustment for demographic characteristics, diet, lifestyle, medication use and medical history. No association was found between Mg intake and PD. Higher Mg intake may be associated with a lower risk of mild cognitive impairment but not necessarily in a dose-response manner. The association between total Mg intake, MCI/PD and MCI were non-linear as suggested by the likelihood test. Although Mg intake from dietary source only did were not significantly associate with MCI/PD, the results appeared to be intuitive because the levels of Mg intake from dietary source was lower than the sum of dietary and supplemental source.

Comparison with previous literature

Our findings were consistent with two previous studies that demonstrated the lowest risk cognitive decline among participants with a moderate Mg intake. Ozawa and colleagues assessed the association between self-reported dietary intake of minerals (potassium, calcium, and magnesium) and dementia risk among Japanese older adults.[9] The hazard ratio for the development of all-cause dementia was 0.63 (95% CI = 0.40–1.01) for the highest quartile (≥196 mg/d) of Mg intake compared to the lowest quartile (≤147 mg/d). For our study, the hazard ratio for the development of probable dementia was also insignificant (HR: 1.05, 95% CI = 0.48–2.29) for the highest quintile (>337.6mg/d) of Mg intake compared to the lowest quintile (<236.9mg/d). In another study from the Netherlands, a "U" shaped distribution in the association between 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, comparing with the lowest quintile, the second quintile of total Mg intake was associated with lowest risk of combined MCI/PD and MCI after adjusting for various confounders. The present findings do support total Mg intake (257.3-317.8 mg/day) between Estimated Average Requirement (estimated nutrient intake to meet the requirement of half the healthy individuals, 265mg/day for women >51 years old) and Recommended Dietary Allowances (sufficient average daily dietary intake level to meet the nutrient requirement of 97 to 98% healthy individuals, 320mg/day for women >51 years old) is optimal for preventing cognitive decline,[44, 45] while further increment of Mg intake did not provide additional benefit. Another observation is that total Mg intake had similar magnitude of association with MCI/PD and MCI but associated with the risk of PD without statistical significance. In other words, total Mg intake is more

protective against MCI. Since we only assessed the baseline diet, it is possible that long follow-up period weakened the association between Mg intake and dementia.

Strengths and Limitations

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, such as assessing Mg intake at baseline only. However, the test based on the Schoenfeld residuals were statistically insignificant, therefore the impact of Mg intake on MCI and/or PD was less likely to change over time. Moreover, we are lacking information on 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, the primary source of dietary Mg.[46] In addition, previous studies have found that dietary Mg intake might not strongly correlate with serum Mg levels ($r=0.28$, $p<0.05$).[47] That may lead to the different magnitudes of associations, such as the impact of dietary/serum Mg on the risk of a disease, such as described for hypertension.[48] Moreover, supplemental Mg intake was collected for 'other supplement mixtures' and single supplements but not for standard multivitamins with minerals which was the most common type of supplement used by WHI women. Although this limitation might lead to an under-ascertainment of Mg from supplements, whether it was the major flaw of this study was arguable, since the total Mg intake has demonstrated significant association with MCI/PD. Last but not least, the present cohort included only postmenopausal women, and the findings may not be generalizable to elder 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, total Mg intake between Estimated Average Requirement and Recommended Dietary Allowances was associated with lower risk of composite MCI/PD and MCI despite not in a dose-response manner.

Contributors: KL, QL, TM, AHS, LP, XL, JEM, SL searched the literature; analyzed and interpreted the data; and wrote the manuscript. SR, JCC, MN, SS participated in the study design; collected, analyzed, and interpreted the data; and wrote the manuscript.

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Ethics approval: The WHI study was approved by the research ethics committees at each of the participating centers

(https://www.whi.org/about/SitePages/Study%20Organization.aspx).

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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)	<0.01*
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)	0.34
BMI at baseline	28.6 (5.5)	28.5 (5.3)	28.3 (5.4)	28.3 (5.3)	28.3 (5.5)	0.41
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)	<0.01*
Total magnesium intake in mg	153.7 (29.9)	228.2 (17.7)	287.1 (17.6)	355.3 (23)	531.1 (172.3)	<0.01*
Total B6 intake in mg	3.7 (20.3)	5.1 (22.7)	5.7 (18.2)	6.9 (21.2)	12.9 (47.6)	<0.01*
Total B9 intake in mcg	219.2 (144.3)	349.5 (227.7)	451.3 (195.4)	569.3 (215)	698.8 (278.9)	<0.01*
Total B12 intake in mcg	12 (54.5)	17.3 (83.7)	16.2 (51.9)	19.5 (54.8)	37.3 (102.9)	<0.01*
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)	<0.01*
Total vitamin D intake in mcg	3.9 (3.9)	6.7 (4.8)	9.4 (5.3)	11.8 (5.4)	15.5 (7.1)	<0.01*
Dietary energy in kcal	1080.1 (306.1)	1375.4 (365)	1589.4 (444.6)	1845 (537.6)	2135.7 (758)	<0.01*
Region in U.S.						
Northeast	336 (26.0%)	377 (29.1%)	365 (28.2%)	333 (25.7%)	360 (27.8%)	0.17
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%)	<0.01*
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%)	<0.01*
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%)	<0.01*
Prevalent diabetes	107 (8.3%)	112 (8.7%)	92 (7.1%)	93 (7.2%)	103 (8.0%)	0.51
Prevalent cardiovascular disease	196 (15.4%)	236 (18.5%)	212 (16.6%)	198 (15.5%)	241 (18.8%)	0.05*
Prevalent cancer	54 (4.2%)	42 (3.3%)	43 (3.3%)	50 (3.9%)	43 (3.3%)	0.63
Hormone Replacement Therapy						0.31
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%)	0.65
History of hypertension	497 (38.9%)	528 (41.1%)	498 (38.7%)	455 (35.5%)	514 (40.0%)	0.05*
Family history of diabetes, heart attack or stroke	983 (76.0%)	999 (77.1%)	1024 (79.1%)	1003 (77.5%)	982 (75.9%)	0.29
Medication use [a]	594 (45.9%)	610 (47.1%)	592 (45.7%)	592 (45.7%)	621 (48.0%)	0.70
Smoking status						<0.01*
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%)	
Received college education or above	622 (48.3%)	698 (54%)	795 (61.5%)	817 (63.1%)	829 (64.4%)	<0.01*

Q: Quintile MCI: mild cognitive impairment; PD: probable dementia; HRT: Hormone replacement therapy; E-alone: Estrogen-alone:E+P:Estrogen+Progestin * *P* value < 0.05 [a] Any use of anti-inflammatory, anti-hyperlipidemic, anti-depressant, anti-hypertensive or diuretic drug

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

	Cases/Total	N=6,473		N=6,183	
		Model 1 HR (95% CI) [a]	p value	Model 2 HR (95% CI) [b]	p value
MCI/PD					
Total magnesium intake by quintiles			0.01*[c]		0.42 [c]
Q1 (<197.4 mg/day)	184/1294	Ref		Ref	
Q2 (197.4-257.3 mg/day)	157/1295	0.82 (0.66, 1.02)	0.08	0.86 (0.68, 1.08)	0.20
Q3 (257.3-317.8 mg/day)	134/1295	0.65 (0.52, 0.81)	<0.01***	0.69 (0.53, 0.91)	0.01*
Q4 (317.8-398.7 mg/day)	142/1295	0.73 (0.59, 0.92)	0.01*	0.77 (0.57, 1.05)	0.10
Q5 (>398.7 mg/day)	148/1294	0.73 (0.59, 0.91)	0.01*	0.81 (0.57, 1.17)	0.27
Mild Cognitive Impairment					
Total magnesium intake by quintiles			<0.01** [c]		0.06 [c]
Q1 (<197.4 mg/day)	131/1294	Ref		Ref	
Q2 (197.4-257.3 mg/day)	106/1295	0.79 (0.61, 1.02)	0.07	0.77 (0.58, 1.03)	0.08
Q3 (257.3-317.8 mg/day)	87/1295	0.61 (0.47, 0.81)	<0.01**	0.63 (0.45, 0.87)	0.01*
Q4 (317.8-398.7 mg/day)	91/1295	0.71 (0.54, 0.93)	0.01*	0.67 (0.46, 0.97)	0.04*
Q5 (>398.7 mg/day)	90/1294	0.66 (0.50, 0.86)	<0.01**	0.61 (0.39, 0.96)	0.03*
Probable dementia					
Total magnesium intake by quintiles			0.76 [c]		0.29 [c]
Q1 (<197.4 mg/day)	81/1294	Ref		Ref	
Q2 (197.4-257.3 mg/day)	77/1295	0.89 (0.65, 1.22)	0.48	1.02 (0.73, 1.44)	0.90
Q3 (257.3-317.8 mg/day)	72/1295	0.76 (0.55, 1.05)	0.10	0.87 (0.60, 1.28)	0.49
Q4 (317.8-398.7 mg/day)	80/1295	0.86 (0.63, 1.18)	0.36	1.06 (0.69, 1.63)	0.80
Q5 (>398.7 mg/day)	85/1294	0.92 (0.68, 1.26)	0.61	1.25 (0.75, 2.08)	0.39

[a] Model 1 adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status.

[b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline [c] p-value for trend. *p<0.05. **p<0.01 ***p<0.001.

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

	Cases/Total	N=6,473		N=6,183	
		Model 1 HR (95% CI) [a]	p value	Model 2 HR (95% CI) [b]	p value
MCI/PD					
Dietary magnesium intake by quintiles			0.03*[c]		0.34 [c]
Q1 (<170.1 mg/day)	168/1294	Ref		Ref	
Q2 (170.1-216.1 mg/day)	160/1295	0.93 (0.75, 1.16)	0.53	0.96 (0.76, 1.22)	0.73
Q3 (216.1-263.2 mg/day)	144/1295	0.84 (0.67, 1.05)	0.13	0.86 (0.66, 1.12)	0.26
Q4 (263.2-323.3 mg/day)	144/1295	0.79 (0.63, 0.99)	0.04*	0.84 (0.63, 1.13)	0.25
Q5 (>323.3 mg/day)	149/1294	0.81 (0.65, 1.01)	0.07	0.86 (0.59, 1.24)	0.42
Mild Cognitive Impairment					
Dietary magnesium intake by quintiles			0.01* [c]		0.11 [c]
Q1 (<170.1 mg/day)	118/1294	Ref		Ref	
Q2 (170.1-216.1 mg/day)	111/1295	0.95 (0.73, 1.23)	0.69	0.97 (0.73, 1.29)	0.85
Q3 (216.1-263.2 mg/day)	99/1295	0.87 (0.66, 1.14)	0.32	0.85 (0.62, 1.17)	0.33
Q4 (263.2-323.3 mg/day)	89/1295	0.76 (0.57, 1.00)	0.05	0.78 (0.55, 1.13)	0.19
Q5 (>323.3 mg/day)	88/1294	0.73 (0.55, 0.97)	0.03*	0.71 (0.45, 1.14)	0.16
Probable dementia					
Dietary magnesium intake by quintiles			0.92 [c]		0.66 [c]
Q1 (<170.1 mg/day)	76/1294	Ref		Ref	
Q2 (170.1-216.1 mg/day)	77/1295	0.95 (0.69, 1.31)	0.75	1.00 (0.70, 1.42)	0.98
Q3 (216.1-263.2 mg/day)	71/1295	0.86 (0.62, 1.19)	0.37	0.97 (0.66, 1.41)	0.86
Q4 (263.2-323.3 mg/day)	86/1295	0.97 (0.71, 1.33)	0.86	1.11 (0.74, 1.67)	0.61
Q5 (>323.3 mg/day)	85/1294	0.96 (0.70, 1.31)	0.79	1.08 (0.64, 1.81)	0.78

[a] Model 1 adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status. [b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline [c] p-value for trend. *p<0.05. **p<0.01 ***p<0.001

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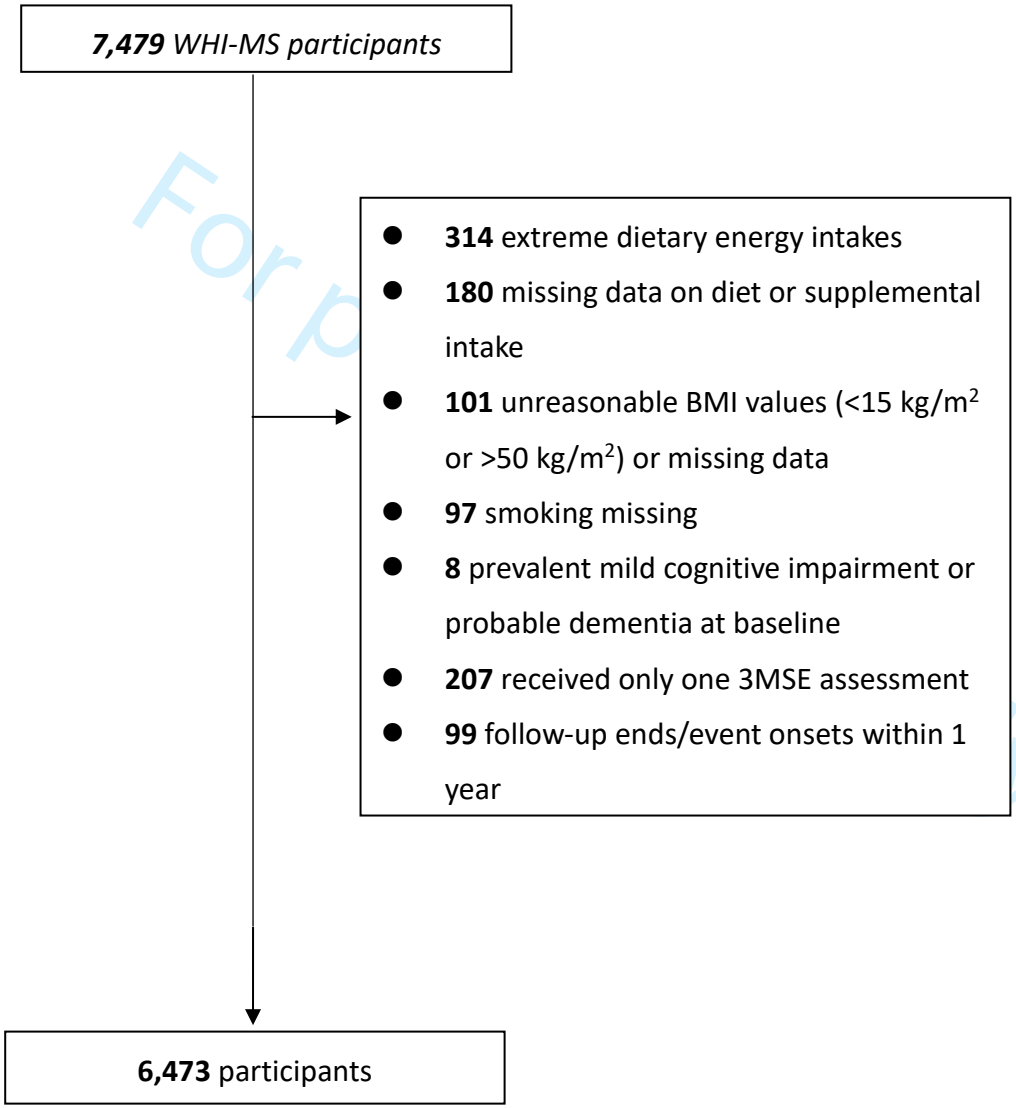
Supplementary Figure 1 Identification of an Analytical Cohort from the Women's Health Initiative Memory Study (WHI-MS)



Supplementary Table 1 Baseline Characteristics of Participants Included or Excluded from Analysis

	Mean (SD) / N (%)		
	Excluded	Included	p value
Number of participants	1006	6473	
Time-to-event/censored in years	5.5 (5.3)	9.6 (4.3)	<0.01*
Age at baseline in years	70.3 (3.9)	70.1 (3.8)	0.05
BMI at baseline	29.5 (7.5)	28.4 (5.4)	<0.01*
Recreational physical activity in MET-hour	10.7 (13.8)	11.3 (13.2)	0.18
Total magnesium intake in mg	251 (162.1)	311.1 (151.2)	<0.01*
Total B6 intake in mg	6.1 (21)	6.8 (28.4)	0.44
Total B9 intake in mcg	374.7 (272.4)	457.6 (273.5)	<0.01*
Total B12 intake in mcg	18.2 (63.6)	20.5 (73)	0.36
Total calcium intake in mg	871.3 (689.7)	1139.2 (698.8)	<0.01*
Total vitamin D intake in mcg	7.2 (6.5)	9.5 (6.7)	<0.01*
Dietary energy in kcal	1344.9 (976.7)	1605.1 (625.3)	<0.01*
Region in U.S.			
● Northeast	234 (23.3%)	1771 (27.4%)	<0.01*
● South	263 (26.1%)	1315 (20.3%)	
● Midwest	208 (20.7%)	1598 (24.7%)	
● West	301 (29.9%)	1789 (27.6%)	
Race/Ethnicity			<0.01*
● Non-Hispanic White	810 (80.7%)	5683 (88.0%)	
● Black or African-American	120 (12.0%)	415 (6.4%)	
● Hispanic/Latino	35 (3.5%)	144 (2.2%)	
● Other	39 (3.9%)	217 (3.4%)	
HRT Arm			<0.01*
● E-alone	221 (22.0%)	1248 (19.3%)	
● E-alone control	227 (22.6%)	1257 (19.4%)	
● E+P intervention	289 (28.7%)	1935 (29.9%)	
● E+P control	269 (26.7%)	2033 (31.4%)	
7+ alcohol drinks per week	83 (8.5%)	810 (12.6%)	<0.01*
Prevalent diabetes	120 (12.0%)	507 (7.8%)	<0.01*
Prevalent cardiovascular disease	204 (20.8%)	1083 (17.0%)	<0.01*
Prevalent cancer	35 (3.6%)	232 (3.6%)	0.93
Hormone Replacement Therapy			0.57
● Never used	702 (69.8%)	4444 (68.7%)	
● Past user	254 (25.2%)	1657 (25.6%)	
● Current user	50 (5.0%)	372 (5.7%)	
Treated high cholesterol	194 (19.8%)	1151 (18.0%)	0.16
History of hypertension	424 (43.4%)	2492 (38.8%)	0.01*

Family history of diabetes, heart attack or stroke	768 (76.3%)	4991 (77.1%)	0.59
Medication use [a]	510 (50.7%)	3009 (46.5%)	0.01*
Smoking status			<0.01*
● Never Smoked	463 (51.7%)	3446 (53.2%)	
● Past Smoker	333 (37.2%)	2597 (40.1%)	
● Current Smoker	99 (11.1%)	430 (6.6%)	
Received college education or above	514 (51.2%)	3761 (58.3%)	<0.01*

MCI: mild cognitive impairment; PD: probable dementia; HRT: Hormone replacement therapy; E-alone: Estrogen-alone:E+P:Estrogen+Progestin

* *P* value < 0.05 [a] Any use of anti-inflammatory, anti-hyperlipidemic, anti-depressant, anti-hypertensive or diuretic drug

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	15
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	17-18

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	17-18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

BMJ Open

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 in aging women.

Design: A Prospective Cohort Study of participants enrolled in the Women's Health Initiative Memory Study (WHIMS) which extended and named WHIMS-Epidemiology of Cognitive Health (WHIMS-ECHO).

Setting: 40 Clinical Centers in United States.

Participants: Postmenopausal women aged 65 to 79 years without dementia at enrolment.

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

Results: After excluding 1,006 women who had extreme values of dietary energy intake, had missing or extreme BMI values, with prevalent MCI/PD at baseline, received only one cognitive assessment, or had been followed-up for less than one year. During > 20 years of follow-up, 765 (11.8%) out of 6,473 participants developed MCI/PD. For MCI/PD and MCI, the risks tended to be lower among participants in quintiles Q2 to Q5 of Mg consumption compared with those in the lowest quintile. Participants in Q3 had a significant lower risk of MCI/PD (HR = 0.69, 95% CI 0.53-0.91) and MCI (0.63, 0.45-0.87), after adjustment for covariates of demographics, diet, lifestyle, medication use, and medical history. No significant association was observed between total Mg intake and PD. The association between total Mg intake, MCI/PD and MCI were 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: clinicaltrials.gov (NCT00685009)

Strengths and limitations of this study

- A large prospective cohort with long follow-up, and careful adjudication of MCI/PD events to ensure a high quality of outcome assessment.
- Lacking information on serum Mg levels in the studied population.
- The present cohort included only postmenopausal women, and the findings may not be generalizable to elder men.

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 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 has interfered with daily function.(2) Dementia affects approximately 47 million people worldwide, and its prevalence is expected to more than triple by 2050.(3) The prevalence of dementia and associated medical costs have increased dramatically in recent years in parallel with the aging population globally, which has increased the healthcare burden to communities, families and individuals.(3) Compared to older men, older 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 of to prevent vascular outcomes. Recent work has shown that magnesium may regulate N-methyl-D-aspartate (NMDA)

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

Methods

Data source

The WHI Memory Study (WHIMS) is an ancillary study to the WHI Hormone Trial (N=27,347 for the whole trial) that was 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 who were aged 65 to 79 years and without dementia at enrolment.(12) Following the termination of the HT intervention, the WHIMS (1995-2008, 7,479 participants) and subsequent WHIMS-Epidemiology of Cognitive Health (ECHO) follow-up (2008 onwards, ~2900 participants) continued annual assessments of cognitive function and adjudication of all-cause dementia and MCI status. The ethical approval of all protocols was obtained from the institutional review boards (IRBs) of all participating institutions (40 clinical

site IRBs, the coordinating center IRB and ethical review at National Institutes of Health). Written informed consent was obtained from participants.

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 kcal or >5000 kcal), missing or extreme BMI values (BMI<15 kg/m^2 or BMI>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 dietary intake and disease onset, we only included women who had been followed-up for at least one year. The detailed participant selection is illustrated in **Supplementary Figure 1**.

Outcome Variable

The WHIMS and WHIMS-ECHO protocol used a multi-phase approach to identify cases of MCI and PD. From 1995 through 2007 (WHIMS), participants were screened annually in clinic by trained and certified examiners using the Modified Mini- Mental State Examination (3MSE). The 3MSE ranges from 0 to 100, and the initial cut-points for further testing were 72 or lower for participants with <9 years of education, and 76 or lower for participants with 9 years or more of education. After 1st July 1998, the cut points were 80 and 88, respectively. Participants who scored below the education-adjusted 3MSE cut-points received the in-depth multi-phased evaluation,(13) including a battery of neuropsychological tests, history and physical, neuropsychiatric evaluation, and an interview of friend or family member to assess functional status(11).

Beginning in 2008 (WHIMS-ECHO), an annual validated cognitive test battery that included the Telephone Interview for Cognitive Status-modified (TICSm)(14) and other validated tests of cognitive function were administered by telephone. (15) To justify replacing 3MSE assessment with TICSm, a validation study was conducted. Results showed that the 3MSE scores predicted by TICSm was highly correlated (0.82) with 3MSE scores,(16) while the transformation of WHIMS 3MSE and WHIMS-ECHO TICSm data into relative percentile ranks fit the trajectories of global cognitive function.(17) For women who were screened positive (i.e., TICSm<31) during WHIMS-ECHO follow-up, a reliable and pre-identified informant was interviewed by telephone using the standardized Dementia Questionnaire to assess the history of cognitive and behavioral 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 center. The committee had experts experienced in neurological examinations and neuropsychiatric evaluations, where cases are classified as no impairment, MCI or PD. (19) Outcome classification was based on the DSM-IV 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 food frequency questionnaire (FFQ).(21) The nutrient database for the WHI FFQ uses the Nutrition Data Systems for Research (NDS-R, version 2005, University of Minnesota Nutrition Coordinating Center, Minneapolis, MN) food and nutrient database.(22) The data on 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, which has demonstrated high correlation (ranged from 0.8 to 1.0) with photo-copied labels in 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, levels of Mg intake were categorized into quintiles.

Covariates

At WHI baseline, WHIMS participants completed questionnaires on various information, including demographics (age, race-ethnicity), socioeconomic status (education in years), lifestyle factors (diet, smoking, alcohol use, 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, anti-hyperlipidemia drugs, anti-depressants, anti-hypertensive drugs or diuretics). Height and weight were measured at baseline for calculating Body Mass Index (BMI).

Data analysis

Descriptive statistics were demonstrated by the quintiles of total magnesium intake. The differences between quintiles were tested by one-way ANOVA for continuous variables and chi-square 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 hazard ratios (HRs) and associated 95% confidence intervals (95% CI). 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 end-point of MCI/PD was presented as a combined end-point in primary analyses. MCI and PD were treated as secondary end-points respectively. The event time was defined as the time of screening by global cognitive tests (either 3MS or TICSm) that triggered the subsequent work-up that concluded with the central adjudication of first MCI/PD. If a participant had progressed from MCI to PD, she was classified as a case of PD instead of MCI. The test for linear relationship was conducted by assigning median values for quintiles, then treated it as a continuous variable in regression model. To examine the potential non-linear relationship between 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, hence a non-linear relationship between Mg intake and cognitive outcomes. To test the assumption of Cox proportional hazards model, we examined all models using the Schoenfeld residual test. A sensitivity analysis was performed by using dietary Mg intake only.

To ensure robustness of regression analysis, we have controlled for confounders with reference to previous studies of cognitive decline. Model 1 was the minimally adjusted model and included age at baseline, region in U.S., race/ethnicity, assignment arm of HT trial, BMI at baseline(28) and smoking status.(29) Model 2 included covariates in Model 1 plus education,(30) dietary variables and physical activity (alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, total intake of calcium and vitamin D),(27, 31-34) as well as 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 (includes cardiac arrest, congestive heart failure, cardiac catheterization, coronary bypass surgery, angioplasty of coronary arteries, carotid endarterectomy/angioplasty, atrial fibrillation or aortic aneurysm)(36) and 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, medication use (anti-inflammatory drugs, anti-hyperlipidemia drugs, anti-depressants, anti-hypertensive 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 3.6.0. P values less than 0.05 were considered statistically significant.

Patient and public involvement

No patients were involved in the design process of this study, setting 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 6,473 participants were included in the analyses. The baseline characteristics of participants in the 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 chisquared test, Non-Hispanic White women, participants enrolled in the control group of the Estrogen+Progestin trial, with ≥ 7 alcohol drinks per week, with a history of cardiovascular disease, being a past smoker or receiving post-college 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 was compared in **Supplementary Table 1**. Between-group difference was significant for the majority of variables except for baseline age, recreational physical activity, total B6 and B12 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 Mild Cognitive Impairment/Probable Dementia

Table 2 illustrates the association between total Mg intake and risk of MCI and/or PD. A total of 505 (7.8%) women developed MCI across the increasing quintiles of total Mg intake, while 395 (6.1%) women developed PD. When using the lowest quintile as the referent, the third quintile of total Mg intake was associated with risk of composite MCI/PD (HR = 0.69, 95% CI = 0.53, 0.91, p=0.01) in the fully adjusted model. Comparing with the lowest quintile, the third (HR = 0.63, 95% CI = 0.45, 0.87, p=0.01), fourth (HR = 0.67, 95% CI = 0.46, 0.97, p=0.04) and fifth (HR = 0.61, 95% CI = 0.39, 0.96, p=0.03) quintile associated with 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 into the regression model significantly improved the model fit as shown by the likelihood ratio test (both p<0.01), which indicated a non-linear relationship between

total Mg intake and cognitive decline. None of the models in Table 2 violated the assumption of the Cox proportional hazards model.

Dietary Magnesium intake and risk of Mild Cognitive Impairment/Probable Dementia

Table 3 illustrates the association between dietary Mg intake and risk of MCI and/or PD. None of the associations between 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, while 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 dietary Mg intake and cognitive impairment in a geographically diverse cohort of post-menopausal women in a sub-cohort of the WHI. 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 the statistical adjustment for demographic characteristics, diet, lifestyle, medication use and medical history. For MCI/PD and MCI, the HR estimates in Model 1 and Model 2 were similar in magnitude, the lesser significance in Model 2 being might 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 mild cognitive impairment but not necessarily in a dose-response manner. The association between total Mg intake, MCI/PD and MCI were non-linear as suggested by the likelihood test. Although Mg intake only

from the dietary source did not significantly associate with MCI/PD, this may be because the levels of Mg intake from dietary source was lower than the sum of dietary and supplemental source.

Comparison with previous literature

Our findings are consistent with two previous studies that demonstrated the lowest risk cognitive decline among participants with a moderate Mg intake. Ozawa and colleagues assessed the association between self-reported dietary intake of minerals (potassium, calcium, and magnesium) and dementia risk among Japanese older adults.(9) The hazard ratio for the development of all-cause dementia was 0.63 (95% CI = 0.40–1.01) for the highest quartile (≥196 mg/d) of Mg intake compared to the lowest quartile (≤147 mg/d). For our study, the hazard ratio for the development of probable dementia was also not significant (HR: 1.05, 95% CI = 0.48–2.29) for the highest quintile (>337.6mg/d) of Mg intake compared to the lowest quintile (<236.9mg/d). In another study from the Netherlands, a "U" shaped distribution in the association between 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, comparing with the lowest quintile, the second quintile of total Mg intake was associated with lowest risk of combined MCI/PD and MCI after adjusting for various confounders. The present findings do support total Mg intake (257.3-317.8 mg/day) between Estimated Average Requirement (estimated nutrient intake to meet the requirement of half the healthy individuals, 265mg/day for women >51 years old) and Recommended Dietary Allowances (sufficient average daily dietary intake level to meet the nutrient requirement of 97 to 98% healthy individuals, 320mg/day for women >51 years old) is optimal for preventing cognitive decline.(44, 45) Although

further increment of Mg intake did not provide additional benefit for preventing MCI/PD, comparing with the lowest quintile, the fourth and fifth quintile of total Mg intake associated with lower risk of MCI. Another observation is that total Mg intake had similar magnitude of association with MCI/PD and MCI but associated with the risk of PD without statistical significance. In other words, total Mg intake is more protective against MCI. Since we only assessed the baseline diet, it is possible that long follow-up period weakened the association between Mg intake and dementia.

Strengths and Limitations

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, such as assessing Mg intake at baseline only. However, the test based on the Schoenfeld residuals were not statistically significant, therefore the impact of Mg intake on MCI and/or PD was less likely to change over time. Moreover, we are lacking information on 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, the primary source of dietary Mg.(46) In addition, previous studies have found that dietary Mg intake might not strongly correlate with serum Mg levels ($r=0.28$, $p<0.05$).(47) That may lead to the different magnitudes of associations, such as the impact of dietary/serum Mg on the risk of a disease, such as described for hypertension.(48) Moreover, supplemental Mg intake was collected for 'other supplement mixtures' and single supplements but not for standard multivitamins with minerals which was the most common type of supplement used by WHI women. Although this limitation might lead to an under-ascertainment of Mg from

supplements, whether it was the major flaw of this study was arguable, since the total Mg intake has demonstrated significant association with MCI/PD. Furthermore, there might be residual confounding due to inaccuracy of 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 generalizable to elder 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, total Mg intake between Estimated Average Requirement and Recommended Dietary Allowances was associated with lower risk of composite MCI/PD and MCI but not in a dose-response manner.

Contributors: KL, QL, TM, AHS, LP, XL, JEM, SL searched the literature; analyzed and interpreted the data; and wrote the manuscript. SR, JCC, MN, SS participated in the study design; collected, analyzed, and interpreted the data; and wrote the manuscript.

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Ethics approval: The WHI study was approved by the research ethics committees at each of the participating centers (https://www.whi.org/about/SitePages/Study%20Organization.aspx).

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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)	*<0.01***
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)	*0.34*
BMI at baseline	28.6 (5.5)	28.5 (5.3)	28.3 (5.4)	28.3 (5.3)	28.3 (5.5)	*0.41*
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)	*<0.01***
Total magnesium intake in mg	153.7 (29.9)	228.2 (17.7)	287.1 (17.6)	355.3 (23)	531.1 (172.3)	*<0.01***
Total B6 intake in mg	3.7 (20.3)	5.1 (22.7)	5.7 (18.2)	6.9 (21.2)	12.9 (47.6)	*<0.01***
Total B9 intake in mcg	219.2 (144.3)	349.5 (227.7)	451.3 (195.4)	569.3 (215)	698.8 (278.9)	*<0.01***
Total B12 intake in mcg	12 (54.5)	17.3 (83.7)	16.2 (51.9)	19.5 (54.8)	37.3 (102.9)	*<0.01***
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)	*<0.01***
Total vitamin D intake in mcg	3.9 (3.9)	6.7 (4.8)	9.4 (5.3)	11.8 (5.4)	15.5 (7.1)	*<0.01***
Dietary energy in kcal	1080.1 (306.1)	1375.4 (365)	1589.4 (444.6)	1845 (537.6)	2135.7 (758)	*<0.01***
Region in U.S.						
Northeast	336 (26.0%)	377 (29.1%)	365 (28.2%)	333 (25.7%)	360 (27.8%)	*0.17*
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%)	*<0.01***
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%)	*<0.01***
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%)	*<0.01***
Prevalent diabetes	107 (8.3%)	112 (8.7%)	92 (7.1%)	93 (7.2%)	103 (8.0%)	*0.51*
Prevalent cardiovascular disease	196 (15.4%)	236 (18.5%)	212 (16.6%)	198 (15.5%)	241 (18.8%)	*0.05**
Prevalent cancer	54 (4.2%)	42 (3.3%)	43 (3.3%)	50 (3.9%)	43 (3.3%)	*0.63*
Hormone Replacement Therapy						*0.31*
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%)	*0.65*
History of hypertension	497 (38.9%)	528 (41.1%)	498 (38.7%)	455 (35.5%)	514 (40.0%)	*0.05*
Family history of diabetes, heart attack or stroke	983 (76.0%)	999 (77.1%)	1024 (79.1%)	1003 (77.5%)	982 (75.9%)	*0.29*
Medication use [a]	594 (45.9%)	610 (47.1%)	592 (45.7%)	592 (45.7%)	621 (48.0%)	*0.70*
Smoking status						*<0.01****
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%)	
Received college education or above	622 (48.3%)	698 (54%)	795 (61.5%)	817 (63.1%)	829 (64.4%)	*<0.01****

[a] Any use of anti-inflammatory, anti-hyperlipidemic, anti-depressant, anti-hypertensive or diuretic drug. Chi-square (categorical variables) and one-way ANOVA (continuous variables) for subgroup differences: *$p<0.05$. **p<0.01 ***p<0.001.

Abbreviations: Q (Quintile); MCI (mild cognitive impairment); PD (probable dementia); HRT (Hormone replacement therapy); E-alone (Estrogen-alone); E+P (Estrogen plus Progestin).

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

		Model 1 (N=6,473)		Model 2 (N=6,183)	
	Cases/Total	HR (95% CI) [a]	*P* value	HR (95% CI) [b]	*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, 1.02)	*0.08*	0.86 (0.68, 1.08)	*0.20*
Q3 (257.3-317.8 mg/day)	134/1295	0.65 (0.52, 0.81)	*<0.01***	0.69 (0.53, 0.91)	*0.01**
Q4 (317.8-398.7 mg/day)	142/1295	0.73 (0.59, 0.92)	*0.01**	0.77 (0.57, 1.05)	*0.10*
Q5 (>398.7 mg/day)	148/1294	0.73 (0.59, 0.91)	*0.01**	0.81 (0.57, 1.17)	*0.27*
p-value for trend					*0.42*
p-value for non-linearity					*<0.01***
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, 1.02)	*0.07*	0.77 (0.58, 1.03)	*0.08*
Q3 (257.3-317.8 mg/day)	87/1295	0.61 (0.47, 0.81)	*<0.01***	0.63 (0.45, 0.87)	*0.01**
Q4 (317.8-398.7 mg/day)	91/1295	0.71 (0.54, 0.93)	*0.01**	0.67 (0.46, 0.97)	*0.04**
Q5 (>398.7 mg/day)	90/1294	0.66 (0.50, 0.86)	*<0.01***	0.61 (0.39, 0.96)	*0.03**
p-value for trend					*0.06*
p-value for non-linearity					*<0.01***
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, 1.22)	*0.48*	1.02 (0.73, 1.44)	*0.90*
Q3 (257.3-317.8 mg/day)	72/1295	0.76 (0.55, 1.05)	*0.10*	0.87 (0.60, 1.28)	*0.49*
Q4 (317.8-398.7 mg/day)	80/1295	0.86 (0.63, 1.18)	*0.36*	1.06 (0.69, 1.63)	*0.80*
Q5 (>398.7 mg/day)	85/1294	0.92 (0.68, 1.26)	*0.61*	1.25 (0.75, 2.08)	*0.39*
p-value for trend					*0.29*
p-value for non-linearity					*0.99*

[a] Model 1 adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status.

[b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline *p<0.05. **p<0.01 ***p<0.001.

Abbreviations: Mild Cognitive Impairment (MCI), Probable Dementia (PD).

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

		Model 1 (N=6,473)		Model 2 (N=6,183)	
	Cases/Total	HR (95% CI) [a]	p value	HR (95% CI) [b]	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, 1.16)	*0.53*	0.96 (0.76, 1.22)	*0.73*
Q3 (216.1-263.2 mg/day)	144/1295	0.84 (0.67, 1.05)	*0.13*	0.86 (0.66, 1.12)	*0.26*
Q4 (263.2-323.3 mg/day)	144/1295	0.79 (0.63, 0.99)	*0.04**	0.84 (0.63, 1.13)	*0.25*
Q5 (>323.3 mg/day)	149/1294	0.81 (0.65, 1.01)	*0.07*	0.86 (0.59, 1.24)	*0.42*
p-value for trend					*0.34*
p-value for non-linearity					*0.25*
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, 1.23)	*0.69*	0.97 (0.73, 1.29)	*0.85*
Q3 (216.1-263.2 mg/day)	99/1295	0.87 (0.66, 1.14)	*0.32*	0.85 (0.62, 1.17)	*0.33*
Q4 (263.2-323.3 mg/day)	89/1295	0.76 (0.57, 1.00)	*0.05*	0.78 (0.55, 1.13)	*0.19*
Q5 (>323.3 mg/day)	88/1294	0.73 (0.55, 0.97)	*0.03**	0.71 (0.45, 1.14)	*0.16*
p-value for trend					*0.11*
p-value for non-linearity					*0.64*
PD					
Dietary magnesium intake by quintiles					
Q1 (<170.1 mg/day)	76/1294	Ref		Ref	
Q2 (170.1-216.1	77/1295	0.95 (0.69, 1.31)	*0.75*	1.00 (0.70, 1.42)	*0.98*

mg/day)					
Q3 (216.1-263.2 mg/day)	71/1295	0.86 (0.62, 1.19)	*0.37*	0.97 (0.66, 1.41)	*0.86*
Q4 (263.2-323.3 mg/day)	86/1295	0.97 (0.71, 1.33)	*0.86*	1.11 (0.74, 1.67)	*0.61*
Q5 (>323.3 mg/day)	85/1294	0.96 (0.70, 1.31)	*0.79*	1.08 (0.64, 1.81)	*0.78*
p-value for trend					*0.66*
p-value for non-linearity					*0.30*

[a] Model 1 adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status.

[b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline *p<0.05. **p<0.01 ***p<0.001.

Abbreviations: Mild Cognitive Impairment (MCI), Probable Dementia (PD).

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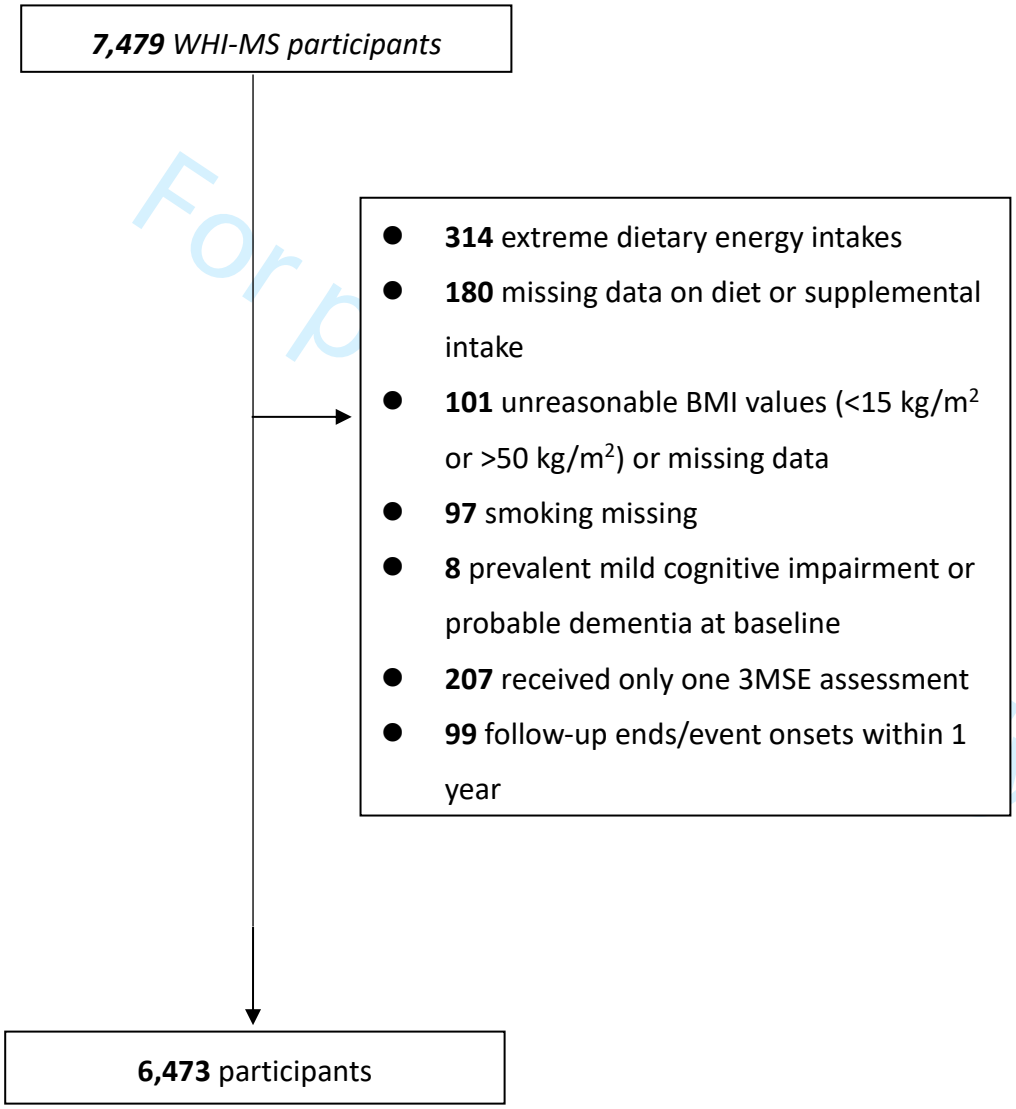
Supplementary Figure 1 Identification of an Analytical Cohort from the Women's Health Initiative Memory Study (WHI-MS)



Supplementary Table 1 Baseline Characteristics of Participants Included or Excluded from Analysis

	Mean (SD) / N (%)		
	Excluded	Included	p value
Number of participants	1006	6473	
Time-to-event/censored in years	5.5 (5.3)	9.6 (4.3)	<0.01***
Age at baseline in years	70.3 (3.9)	70.1 (3.8)	0.05
BMI at baseline	29.5 (7.5)	28.4 (5.4)	<0.01***
Recreational physical activity in MET-hour	10.7 (13.8)	11.3 (13.2)	0.18
Total magnesium intake in mg	251 (162.1)	311.1 (151.2)	<0.01***
Total B6 intake in mg	6.1 (21)	6.8 (28.4)	0.44
Total B9 intake in mcg	374.7 (272.4)	457.6 (273.5)	<0.01***
Total B12 intake in mcg	18.2 (63.6)	20.5 (73)	0.36
Total calcium intake in mg	871.3 (689.7)	1139.2 (698.8)	<0.01***
Total vitamin D intake in mcg	7.2 (6.5)	9.5 (6.7)	<0.01***
Dietary energy in kcal	1344.9 (976.7)	1605.1 (625.3)	<0.01***
Region in U.S.			
● Northeast	234 (23.3%)	1771 (27.4%)	<0.01***
● South	263 (26.1%)	1315 (20.3%)	
● Midwest	208 (20.7%)	1598 (24.7%)	
● West	301 (29.9%)	1789 (27.6%)	
Race/Ethnicity			<0.01***
● Non-Hispanic White	810 (80.7%)	5683 (88.0%)	
● Black or African-American	120 (12.0%)	415 (6.4%)	
● Hispanic/Latino	35 (3.5%)	144 (2.2%)	
● Other	39 (3.9%)	217 (3.4%)	
HRT Arm			<0.01**
● E-alone	221 (22.0%)	1248 (19.3%)	
● E-alone control	227 (22.6%)	1257 (19.4%)	
● E+P intervention	289 (28.7%)	1935 (29.9%)	
● E+P control	269 (26.7%)	2033 (31.4%)	
7+ alcohol drinks per week	83 (8.5%)	810 (12.6%)	<0.01***
Prevalent diabetes	120 (12.0%)	507 (7.8%)	<0.01***
Prevalent cardiovascular disease	204 (20.8%)	1083 (17.0%)	<0.01**
Prevalent cancer	35 (3.6%)	232 (3.6%)	0.93
Hormone Replacement Therapy			0.57
● Never used	702 (69.8%)	4444 (68.7%)	
● Past user	254 (25.2%)	1657 (25.6%)	
● Current user	50 (5.0%)	372 (5.7%)	
Treated high cholesterol	194 (19.8%)	1151 (18.0%)	0.16
History of hypertension	424 (43.4%)	2492 (38.8%)	0.01**

Family history of diabetes, heart attack or stroke	768 (76.3%)	4991 (77.1%)	0.59
Medication use [a]	510 (50.7%)	3009 (46.5%)	0.01*
Smoking status			<0.01***
● Never Smoked	463 (51.7%)	3446 (53.2%)	
● Past Smoker	333 (37.2%)	2597 (40.1%)	
● Current Smoker	99 (11.1%)	430 (6.6%)	
Received college education or above	514 (51.2%)	3761 (58.3%)	<0.01***

MCI: mild cognitive impairment; PD: probable dementia; HRT: Hormone replacement therapy; E-alone: Estrogen-alone:E+P:Estrogen+Progestin

*$p<0.05$. **p<0.01 ***p<0.001. [a] Any use of anti-inflammatory, anti-hyperlipidemic, anti-depressant, anti-hypertensive or diuretic drug

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	15
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	17-18

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	17-18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

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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 amongst 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 (WHIMS-ECHO).

Setting: Forty clinical centres in United States.

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

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

Results: Participants were excluded (N=1,006) 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 less than 1 year. During >20 years of follow-up, 765 (11.8%) out of 6,473 participants developed MCI/PD. For MCI/PD and MCI, the risks tended to be lower among participants in quintiles Q2 to Q5 of Mg consumption compared with those in the lowest quintile. Participants in Q3 had a significantly lower risk of MCI/PD (hazard ratio = 0.69, 95% confidence interval 0.53–0.91) and MCI (0.63, 0.45–0.87) after multivariate adjustments. No significant association was observed between total Mg intake and PD. The association between total Mg intake, MCI/PD and MCI were nonlinear 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: clinicaltrials.gov (NCT00685009)

Strengths and limitations of this study:

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

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 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 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

The WHI Memory Study (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 upon enrolment.(12) Following the termination of the HT intervention, the WHIMS (1995–2008, 7,479 participants) and subsequent WHIMS-Epidemiology of Cognitive Health (ECHO) follow-up (2008 onwards, ~2900 participants) continued the annual assessments of cognitive function and adjudication of all-cause dementia and MCI status. Ethical approval of all protocols was obtained from the institutional review boards (IRBs) of all participating institutions (40 clinical site IRBs, the coordinating centre IRB and ethical review at the National Institutes of Health). 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 kcal or >5000 kcal), missing or

extreme body mass index (BMI) values (BMI <15 kg/m^2 or BMI >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 **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 Modified Mini-Mental State Examination (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 (i.e. TICSm<31) during the WHIMS-ECHO follow-up, a reliable and pre-identified 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 DSM-IV 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, version 2005, University of Minnesota Nutrition Coordinating Center, Minneapolis, MN) 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, anti-hyperlipidaemia 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 ANOVA for continuous variables and chi-squared 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 hazard ratios (HRs) and associated 95% confidence intervals (95% CI). 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 endpoint was presented as a combined endpoint in the primary analyses. MCI and PD were treated as secondary endpoints. The event time was defined as the time of screening by global cognitive tests (either 3MS or TICSm) that triggered the subsequent work-up 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 nonlinear 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 nonlinear 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 U.S., 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 B6/9/12, total intake of calcium and vitamin D),(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, anti-hyperlipidaemia 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 3.6.0. P values less than 0.05 were considered 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 6,473 participants were included in the analyses. The baseline characteristics of participants in the 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 chi-squared test, non-Hispanic white women, participants enrolled in the control group of the estrogen+progestin trial, consumed ≥7 alcohol drinks per week, with a history of cardiovascular disease, were former smokers or receiving post-college education were more likely to have a higher level of Mg intake. The baseline characteristics of participants included (N = 6,473) or excluded (N = 1,006) from the analysis are compared in **Supplementary Table 1**. Between-group difference was significant for the majority of variables except for baseline age, recreational physical activity, total B6 and B12 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%) 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, 0.91, p = 0.01) in the fully adjusted model. Compared with the lowest quintile, the third (HR = 0.63, 95% CI = 0.45, 0.87, p = 0.01), fourth (HR = 0.67, 95% CI = 0.46, 0.97, p=0.04) and fifth (HR = 0.61, 95% CI = 0.39, 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 nonlinear 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 post-menopausal women in a WHI sub-cohort. 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 mild cognitive impairment but not necessarily in a dose-response manner. The association between the total Mg intake, MCI/PD and MCI were nonlinear, 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 and colleagues 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 = 0.40–1.01) 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: 1.05, 95% CI = 0.48–2.29) for the highest quintile (>337.6 mg/day) of Mg intake compared with the lowest quintile (<236.9 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 >51 years old) and Recommended Dietary Allowances (sufficient average daily dietary intake level to meet the nutrient requirement of 97% to 98% healthy individuals; 320 mg/day for women >51 years old) 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 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.

Contributors: KL, QL, TM, AHS, LP, XL, JEM, SL searched the literature; analyzed and interpreted the data; and wrote the manuscript. SR, JCC, MN, SS participated in the study design; collected, analyzed, and interpreted the data; and wrote the manuscript.

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Ethics approval: The WHI study was approved by the research ethics committees at each of the participating centers (https://www.whi.org/about/SitePages/Study%20Organization.aspx).

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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 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 intake in mcg	219.2 (144.3)	349.5 (227.7)	451.3 (195.4)	569.3 (215)	698.8 (278.9)	***
Total B12 intake in mcg	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 mcg	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 U.S.						
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*
Hormone Replacement Therapy						*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 [a]	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%)	
Received college education or above	622 (48.3%)	698 (54%)	795 (61.5%)	817 (63.1%)	829 (64.4%)	***

[a] Any use of anti-inflammatory, anti-hyperlipidemic, anti-depressant, anti-hypertensive or diuretic drug. Chi-square (categorical variables) and one-way ANOVA (continuous variables) for subgroup differences: *p<0.05. **p<0.01 ***p<0.001.

Abbreviations: Q (Quintile); MCI (mild cognitive impairment); PD (probable dementia); HRT (Hormone replacement therapy); E-alone (Estrogen-alone); E+P (Estrogen plus Progestin). NS: not significant

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

	Model 1 (N=6,473)			Model 2 (N=6,183)	
	Cases/Total	HR (95% CI) [a]	*P* value	HR (95% CI) [b]	*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, 1.02)	*NS*	0.86 (0.68, 1.08)	*NS*
Q3 (257.3-317.8 mg/day)	134/1295	0.65 (0.52, 0.81)	***	0.69 (0.53, 0.91)	*
Q4 (317.8-398.7 mg/day)	142/1295	0.73 (0.59, 0.92)	*	0.77 (0.57, 1.05)	*NS*
Q5 (>398.7 mg/day)	148/1294	0.73 (0.59, 0.91)	*	0.81 (0.57, 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, 1.02)	*NS*	0.77 (0.58, 1.03)	*NS*
Q3 (257.3-317.8 mg/day)	87/1295	0.61 (0.47, 0.81)	**	0.63 (0.45, 0.87)	*
Q4 (317.8-398.7 mg/day)	91/1295	0.71 (0.54, 0.93)	*	0.67 (0.46, 0.97)	*
Q5 (>398.7 mg/day)	90/1294	0.66 (0.50, 0.86)	**	0.61 (0.39, 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, 1.22)	*NS*	1.02 (0.73, 1.44)	*NS*
Q3 (257.3-317.8 mg/day)	72/1295	0.76 (0.55, 1.05)	*NS*	0.87 (0.60, 1.28)	*NS*
Q4 (317.8-398.7 mg/day)	80/1295	0.86 (0.63, 1.18)	*NS*	1.06 (0.69, 1.63)	*NS*
Q5 (>398.7 mg/day)	85/1294	0.92 (0.68, 1.26)	*NS*	1.25 (0.75, 2.08)	*NS*
p-value for trend					*NS*
p-value for non-linearity					*NS*

[a] Model 1 adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status. [b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidaemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline *p<0.05. **p<0.01 ***p<0.001. Abbreviations: Mild Cognitive Impairment

(MCI), Probable Dementia (PD). NS: not significant

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

		Model 1 (N=6,473)		Model 2 (N=6,183)	
	Cases/Total	HR (95% CI) [a]	p value	HR (95% CI) [b]	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, 1.16)	*NS*	0.96 (0.76, 1.22)	*NS*
Q3 (216.1-263.2 mg/day)	144/1295	0.84 (0.67, 1.05)	*NS*	0.86 (0.66, 1.12)	*NS*
Q4 (263.2-323.3 mg/day)	144/1295	0.79 (0.63, 0.99)	*	0.84 (0.63, 1.13)	*NS*
Q5 (>323.3 mg/day)	149/1294	0.81 (0.65, 1.01)	*NS*	0.86 (0.59, 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, 1.23)	*NS*	0.97 (0.73, 1.29)	*NS*
Q3 (216.1-263.2 mg/day)	99/1295	0.87 (0.66, 1.14)	*NS*	0.85 (0.62, 1.17)	*NS*
Q4 (263.2-323.3 mg/day)	89/1295	0.76 (0.57, 1.00)	*NS*	0.78 (0.55, 1.13)	*NS*
Q5 (>323.3 mg/day)	88/1294	0.73 (0.55, 0.97)	*	0.71 (0.45, 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, 1.31)	*NS*	1.00 (0.70, 1.42)	*NS*
Q3 (216.1-263.2 mg/day)	71/1295	0.86 (0.62, 1.19)	*NS*	0.97 (0.66, 1.41)	*NS*
Q4 (263.2-323.3 mg/day)	86/1295	0.97 (0.71, 1.33)	*NS*	1.11 (0.74, 1.67)	*NS*
Q5 (>323.3 mg/day)	85/1294	0.96 (0.70, 1.31)	*NS*	1.08 (0.64, 1.81)	*NS*
p-value for trend					*NS*
p-value for non-linearity					*NS*

[a] Model 1 adjustment: age at baseline, region in U.S., assignment of hormone therapy trial, BMI at baseline, and smoking status. [b] Model 2 adjustment: covariates in model 1 along with race/ethnicity, education, alcohol intake, energy expenditure from recreational physical activity, total intake of vitamin B6/9/12, 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, anti-hyperlipidaemia drug, anti-depressant, anti-hypertensive drug or the use of diuretics at baseline *p<0.05. **p<0.01 ***p<0.001. Abbreviations: Mild Cognitive Impairment (MCI), Probable Dementia (PD). NS: not significant

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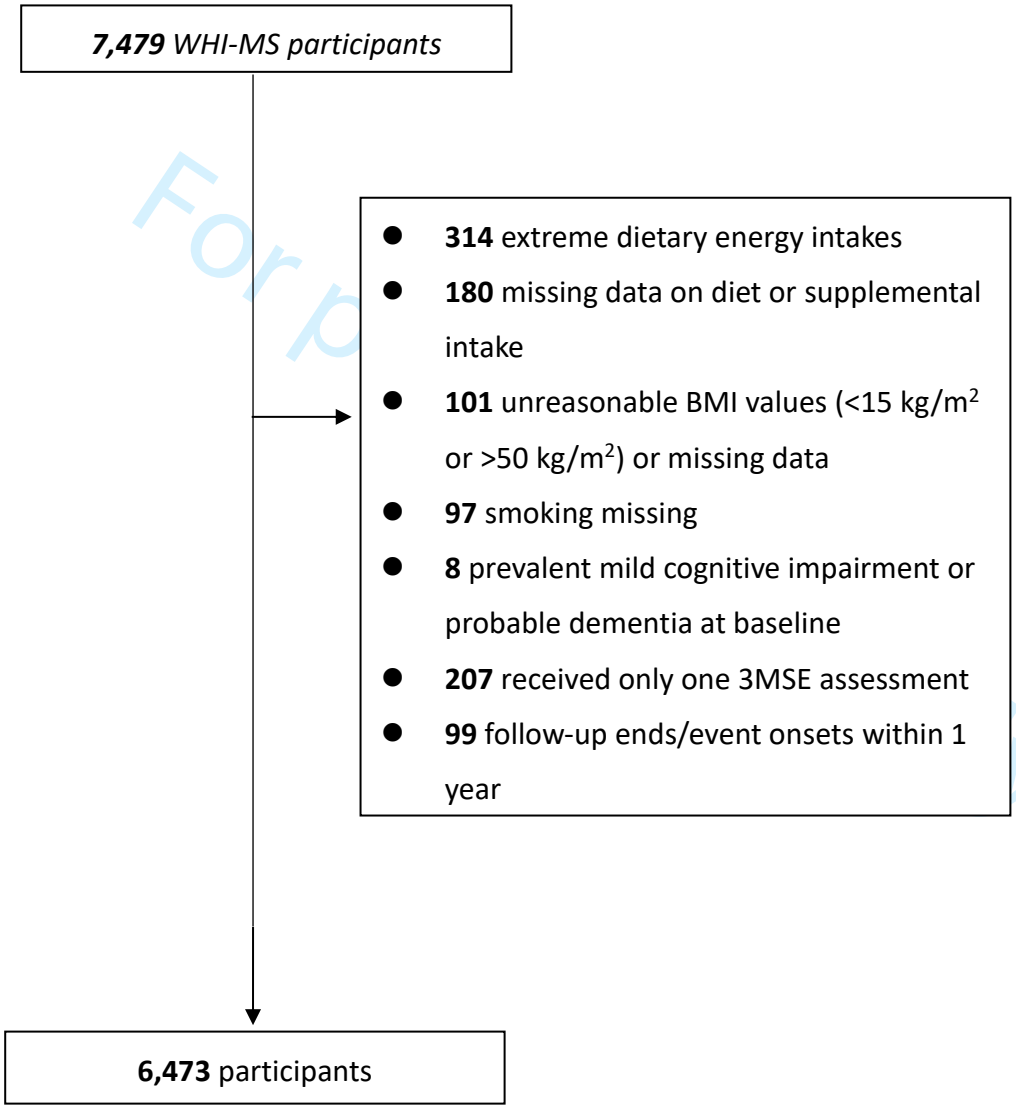
Supplementary Figure 1 Identification of an Analytical Cohort from the Women's Health Initiative Memory Study (WHI-MS)



Supplementary Table 1 Baseline Characteristics of Participants Included or Excluded from Analysis

	Mean (SD) / N (%)		
	Excluded	Included	p value
Number of participants	1006	6473	
Time-to-event/censored in years	5.5 (5.3)	9.6 (4.3)	***
Age at baseline in years	70.3 (3.9)	70.1 (3.8)	NS
BMI at baseline	29.5 (7.5)	28.4 (5.4)	***
Recreational physical activity in MET-hour	10.7 (13.8)	11.3 (13.2)	NS
Total magnesium intake in mg	251 (162.1)	311.1 (151.2)	***
Total B6 intake in mg	6.1 (21)	6.8 (28.4)	NS
Total B9 intake in mcg	374.7 (272.4)	457.6 (273.5)	***
Total B12 intake in mcg	18.2 (63.6)	20.5 (73)	NS
Total calcium intake in mg	871.3 (689.7)	1139.2 (698.8)	***
Total vitamin D intake in mcg	7.2 (6.5)	9.5 (6.7)	***
Dietary energy in kcal	1344.9 (976.7)	1605.1 (625.3)	***
Region in U.S.			
● Northeast	234 (23.3%)	1771 (27.4%)	***
● South	263 (26.1%)	1315 (20.3%)	
● Midwest	208 (20.7%)	1598 (24.7%)	
● West	301 (29.9%)	1789 (27.6%)	
Race/Ethnicity			***
● Non-Hispanic White	810 (80.7%)	5683 (88.0%)	
● Black or African-American	120 (12.0%)	415 (6.4%)	
● Hispanic/Latino	35 (3.5%)	144 (2.2%)	
● Other	39 (3.9%)	217 (3.4%)	
HRT Arm			**
● E-alone	221 (22.0%)	1248 (19.3%)	
● E-alone control	227 (22.6%)	1257 (19.4%)	
● E+P intervention	289 (28.7%)	1935 (29.9%)	
● E+P control	269 (26.7%)	2033 (31.4%)	
7+ alcohol drinks per week	83 (8.5%)	810 (12.6%)	***
Prevalent diabetes	120 (12.0%)	507 (7.8%)	***
Prevalent cardiovascular disease	204 (20.8%)	1083 (17.0%)	**
Prevalent cancer	35 (3.6%)	232 (3.6%)	NS
Hormone Replacement Therapy			NS
● Never used	702 (69.8%)	4444 (68.7%)	
● Past user	254 (25.2%)	1657 (25.6%)	
● Current user	50 (5.0%)	372 (5.7%)	
Treated high cholesterol	194 (19.8%)	1151 (18.0%)	NS
History of hypertension	424 (43.4%)	2492 (38.8%)	**

Family history of diabetes, heart attack or stroke	768 (76.3%)	4991 (77.1%)	NS
Medication use [a]	510 (50.7%)	3009 (46.5%)	*
Smoking status			***
● Never Smoked	463 (51.7%)	3446 (53.2%)	
● Past Smoker	333 (37.2%)	2597 (40.1%)	
● Current Smoker	99 (11.1%)	430 (6.6%)	
Received college education or above	514 (51.2%)	3761 (58.3%)	***

MCI: mild cognitive impairment; PD: probable dementia; HRT: Hormone replacement therapy; E-alone: Estrogen-alone:E+P:Estrogen+Progestin

*p<0.05. **p<0.01 ***p<0.001. NS: not significant [a] Any use of anti-inflammatory, anti-hyperlipidaemic, anti-depressant, anti-hypertensive or diuretic drug

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	15
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	17-18

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	17-18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.