Dietary calcium and magnesium intake and risk for incident dementia: The Shanghai Aging Study

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Abstract

Introduction: Calcium (Ca), magnesium (Mg), or the calcium to magnesium (Ca:Mg) ratio may affect the risk of dementia via complex mechanisms. The aim of this study was to evaluate the association of dietary Ca, Mg, and Ca:Mg ratio with dementia risk at the prospective phase of the Shanghai Aging Study.

Methods: We analyzed data from 1565 dementia-free participants living in an urban community who had measurements of dietary Ca and Mg intake derived from a food frequency questionnaire at baseline and incident dementia during follow-up.

Results: Over the 5-year follow-up, 162 (10.4%) participants were diagnosed with incident dementia by Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria. Participants with the lowest tertile of dietary Ca (<339.1 mg/day) and Mg (<202.1 mg/day) had the highest incidence rates of dementia (3.3/100 person-years for Ca, 3.3/100 person-years for Mg) compared to those with higher Ca and Mg intake.

Conclusions: Our findings suggest that high dietary intake of Mg is associated with an increased risk of dementia mainly among older adults with low Ca:Mg intake ratios.
Proper balance of Ca to Mg in the diet may be critical to the relationship between Mg intake and risk of dementia.

KEYWORDS
aging, calcium, cohort, dementia, dietary, magnesium

Highlights
- Participants with the lowest tertile of dietary calcium (Ca) and magnesium (Mg) had the highest incidence rates of dementia.
- In the subgroup with Ca:Mg ratios ≤1.69, Mg intake >267.5 mg/day was related to an increased risk for dementia.
- Balance of Ca to Mg in diet may be critical to the relationship between Mg intake and risk of dementia.

1 | INTRODUCTION

Nutrients and other dietary components are essential for normal physiological functioning and neuronal protection of the brain. Although research on nutritional risk and protective factors for dementia has emerged over the last two decades, the demand for dietary guidelines for the prevention of cognitive decline and dementia is strong, and novel approaches are still needed.

Some studies have investigated the associations between dietary intake or serum levels of calcium (Ca) and magnesium (Mg), but not their potential interaction, and risk for cognitive decline and dementia but generated inconsistent results. The Ca:Mg dietary intake ratio has been found to modify the association between intakes of Mg and Ca in relation to multiple diseases (e.g., colorectal neoplasia) in US and Western populations with high Ca:Mg ratios (i.e., more intake of dairy products than vegetables, fruits, and seeds). In a recent precision-based double-blinded randomized trial, among those who consumed diets with high Ca:Mg ratios, reducing Ca:Mg ratios significantly improved cognition among individuals >65 years. In contrast to the findings from studies conducted in the United States and in other Western populations that consumed high Ca:Mg diets (median: currently over 3.0), two large-scale cohort studies conducted in Chinese populations that consume diets with low Ca:Mg ratios (median: 1.7; i.e., more intake of vegetables, fruits, and seeds than dairy products) found that dietary intakes of Mg greater than the US Recommended Daily Allowance levels were related to an increased risk of mortality due to cardiovascular disease (CVD). High Mg intake was related to an increased risk of mortality due to CVD among those with Ca:Mg ratios ≤1.7 (hazard ratio [HR] = 1.53, 95% confidence interval [CI]: 1.08–2.16).

Because increased risk of CVD is associated with increased risk of dementia, we hypothesize that among participants with low dietary Ca:Mg ratios, increases in dietary Mg could lead to higher risk of dementia. In particular, we hypothesize that among those with very low Ca:Mg ratios, the risk of dementia will be increased among those with higher Mg dietary intake. We test this hypothesis at the prospective phase of the Shanghai Aging Study (SAS), a study conducted in an older Chinese population with Ca:Mg intake ratios much lower than US and other Western populations (median: 1.7 vs. currently over 3.0).

2 | METHODS

2.1 | Study population

The study methodology of the SAS has been described previously. Participants >60 years were recruited from an urban section of central Shanghai, China (Jing’ansi community) in 2010 and 2011. Inclusion criteria included participants who were permanent residents in the community, not living in nursing homes or other institutions, and could complete the neuropsychological evaluation (thus without psychiatric disorders; severe schizophrenia; and severe impairment in hearing, vision, or language). From April 1, 2014, to December 31, 2016, we conducted the first incidence wave in which participants without dementia at baseline were contacted by research coordinators and invited for follow-up interviews and evaluations.

This study was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. All the participants and/or their legal guardians provided written informed consent to participate in the study.

2.2 | Medical history and other confounding factors

At baseline, we obtained a history of diabetes, hypertension, heart disease, and stroke by combining participants’ self-reports, relevant medication use, and medical records. Other potential confounders related
RESEARCH IN CONTEXT

1. Systematic review: We searched literature in PubMed and found that several studies have investigated the associations between dietary intake of calcium (Ca) or magnesium (Mg) and risk for incident cognitive decline and dementia but generated inconsistent results. However, none of these previous studies investigated the potential interaction between intakes of Mg and Ca in relation to cognitive decline and dementia.

2. Interpretation: In a population with low Ca:Mg ratios, a higher intake of Mg was associated with an increased risk for incident dementia. The proper balance of Ca to Mg in the diet may be critical to the prevention of dementia.

3. Future directions: Guidance on how much Ca and Mg to eat in one’s daily diet may have important implications for cognitive aging and for dietary recommendations made to the public. Future studies are needed to (a) certify the dose–response relationship of intake Ca:Mg ratio and dementia risk by prospective studies with larger sample and longer follow-up period in other populations living in diverse geographic regions, (b) provide solid evidence of recommended diet Ca and Mg by randomized controlled trials with multiple arms, (c) explore the biological mechanism by basic experiments in vivo and in vitro.

2.3 | Measurement of consumption of nutrients

At baseline, usual dietary intake including frequency and portion size over the past 12 months was measured for each participant using an 111-item interviewer-administered food frequency questionnaire (FFQ). The FFQ was designed based on previously validated FFQs that cover common foods consumed in Shanghai, China, such as soyfoods, fermented foods, salted foods, allium-type vegetables, and leafy vegetables. Average daily intakes of dietary Ca and Mg, consumption of other major nutrient intake, and total energy intake, were calculated based on data from the FFQ and the “China Food Composition, 2nd Edition.” For those participants taking nutritional supplements containing Ca and Mg, we also recorded the dose, frequency, and duration of intake of each supplement.

2.4 | Neurological examinations, neuropsychological assessments, and consensus diagnosis

Neurological examinations, neuropsychological battery assessments, and consensus diagnoses were conducted for all participants at both baseline and follow-up interviews.

The neurological examination included motor responses and reflexes, measurement of the Clinical Dementia Rating (CDR) scale, and the Lawton and Brody Activities of Daily Living (ADL) scale. The CDR scale was used to define cognitive complaints if the participants, their informants, or a nurse or physician indicated memory or thinking problems of the participants. A self-reported or informant-reported ADL scale was used to evaluate physical self-maintenance and instrumental activities of daily living, including eating, using the telephone, preparing meals, handling money, and completing chores. Functionally intact was defined if ADL scale > 16.

Neuropsychological assessments covered the domains of global cognition, executive function, spatial construction, memory, language, and attention. Tests used were: (1) Mini-Mental State Examination (MMSE; global cognition), (2) Conflicting Instructions Task (Go/No Go Task; attention), (3) Stick Design Test (visuospatial function), (4) modified Common Objects Sorting Test (language), (5) Auditory Verbal Learning Test (memory), (6) modified Fuld Object Memory Evaluation (memory), (7) Trail-Making Test Parts A and B (executive function), and (8) RMB (Chinese currency) test (executive function). The neuropsychological battery was administered by study psychometrists according to the education level of each participant: Tests (1) to (5) and (7) were used for participants with at least 6 years of education, while tests (1) to (4) and (6) and (8) were used for those with less than 6 years of education. Normative data and a detailed description of these tests are reported elsewhere. All batteries were conducted in Chinese within 90 minutes.

Dementia was diagnosed by a group of neurologists, a neuropsychologist, and a neuroepidemiologist. All functional, medical, neurological, psychiatric, and neuropsychological data were reviewed, and Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria for dementia was reached through consensus diagnosis.

2.5 | Statistical analysis

Analysis of variance (ANOVA) or the Kruskal–Wallis test was used to compare continuous variables, while the Cochran–Mantel–Haenszel chi-squared test was used to compare the categorical variables. Incidence rates of dementia were calculated by dividing the number of new-onset cases by cumulative healthy follow-up person-years. The
time to event was determined as the time from the baseline until the date when dementia was diagnosed (either confirmed by the medical records or evaluated at the follow-up interview) or administrative censoring at the follow-up. The follow-up dates when participants developed disease or were censored were used in the model. Cumulative incidence rates of dementia were estimated using the Kaplan–Meier method and compared using log-rank tests.

The associations of dietary intakes of Ca and Mg with incident dementia, and Ca with dementia by Mg intake levels were estimated using Fine–Gray models to account for the competing risk of death. Stratified analyses were conducted by medians of the Ca:Mg intake ratio. Intakes of Ca and Mg were classified based on the tertile distributions with the lowest tertile as the reference group. Model 1 was a univariate model. Model 2 adjusted for age, sex, education years, APOE ε4, baseline MMSE, total energy intake, dietary Ca intake (Mg model only), and dietary Mg intake (Ca model only). Model 3 additionally adjusted for obesity, smoking, heart disease, stroke, hypertension, diabetes, and CES-D. Model 4 additionally adjusted for the use of nutritional Ca or Mg supplements (yes or no). Association between low versus high Ca:Mg ratio and incident dementia was assessed by the above-mentioned univariate model (Model 1) and multivariate models (Model 2–4).

Two-tailed values of \( P < 0.05 \) were considered statistically significant for all analyses. All statistical analyses were performed using R version 3.5.3.

3 | RESULTS

3.1 | Characteristics of participants at baseline and follow-up

Included in the analysis were 1565 participants with a mean (standard deviation [SD]) follow-up interval of 5.2 ± 0.9 years (Figure 1). The mean age (SD) was 71.1 ± 7.2 years among all participants, and 46.7% were men (\( n = 731 \)). The median Ca:Mg ratio was 1.69. The mean baseline MMSE score was 28.5 ± 1.3. Individuals with higher Mg or Ca intakes were likely to be younger, male, and more likely to have a higher education level. Total energy intake, dietary Ca or Mg, fiber, phosphorus, retinol, vitamin E, sodium, potassium, and zinc were higher in those with higher Mg or Ca intake (Table 1). Participants had an average MMSE score of 27.1 (SD 3.6) at follow-up. The annual incidence of dementia was 2.0/100 person-years in all participants who completed the follow-up interview (Table 1). No significant difference was identified in most characteristics at baseline between participants who were followed up and lost to follow-up (47.6%). Lower prevalence of obesity; higher prevalence of heart disease; and lower MMSE score, intake of total energy, and various nutrients were found in the lost to follow-up group (Table S1 in supporting information).

3.2 | Association between Ca intake and incident dementia

Baseline MMSE score was higher in those with higher dietary Ca intake (Table 1). The incidence of dementia was 3.3/100 person-years for participants with Ca intake less than 339.1 mg/day, 1.4/100 person-years in those with Ca intake between 339.1 and 455.8 mg/day, and 1.4/100 person-years among participants with Ca intake greater than 455.8 mg/day (\( P < 0.01 \)). We found that higher intake of Ca was significantly associated with a reduced risk of incident dementia (\( P < 0.01 \)) in the univariate model. However, after adjusting for baseline MMSE and other potential confounding factors, the significant trend was not found in Models 2, 3, and 4 (Table 2). We did not find a significant association of dietary Ca with dementia by dietary Mg intake levels by the Fine–Gray model (Table S2 in supporting information).

In the stratified analyses by Ca:Mg intake ratio, we found that a higher Ca intake was associated with a reduced risk for incident dementia in participants with Ca:Mg ratios ≤ 1.69 or > 1.69 in the unadjusted Model 1, although the \( P \) for trend was no longer significant after adjusting for confounding factors, including supplemental intake of Ca and Mg (Table 2). As shown in Table S3 in supporting information, no significant association was found between low versus high Ca:Mg ratio and incident dementia, either in the univariate or multivariate models.

3.3 | Association between Mg intake and incident dementia

Baseline MMSE score was higher in individuals with higher dietary Mg intake. The incidence of dementia was 3.3/100 person-years in those with Mg intake < 202.1 mg/day, 1.4/100 person-years in those with Mg intake between 202.1 and 267.5 mg/day, and 1.4/100 person-years with Mg intake > 267.5 mg/day (\( P < 0.01 \); Table 1). A higher intake of Mg was significantly associated with a reduced risk of incident dementia in the univariate model (\( P \) for trend < 0.01). However, after adjusting for baseline MMSE, total energy intake, and other confounding
**TABLE 1** Characteristics at baseline and follow-up of participants grouped by intakes of Ca and Mg

|                          | Ca intake (mg/day) | Mg intake (mg/day) | P-value |
|--------------------------|--------------------|--------------------|---------|
|                          | Total N = 1565     | <339.1 N = 521     | 339.1–455.8 N = 522 | >455.8 N = 522 | P-value |
| Age, mean (SD)           | 71.1 (7.2)         | 73.4 (7.8)         | 70.3 (6.8)         | 69.5 (6.5)      | <0.01   |
| Male, n (%)              | 731 (46.7)         | 216 (41.5)         | 245 (46.9)         | 270 (51.7)      | <0.01   |
| Obesity, n (%)           | 299 (19.1)         | 77 (14.8)          | 113 (21.8)         | 109 (20.9)      | <0.01   |
| Education years, mean (SD)| 12.3 (3.6)        | 11.5 (4.0)         | 12.6 (3.5)         | 12.8 (3.2)      | <0.01   |
| Intensity of occupational activity, n (%) |                     |                    |                    |                  |         |
| Low                      | 1.173 (7.6)        | 361 (71.3)         | 408 (80.3)         | 404 (78.9)      | <0.01   |
| Medium to high           | 353 (23.1)         | 145 (28.7)         | 100 (19.7)         | 108 (21.1)      | <0.01   |
| Current smoker, n (%)    | 159 (10.2)         | 48 (9.2)           | 56 (10.7)          | 55 (10.6)       | 0.70     |
| Diabetes, n (%)          | 206 (13.2)         | 71 (13.6)          | 60 (11.5)          | 75 (14.4)       | 0.36     |
| Hypertension, n (%)      | 831 (53.1)         | 283 (54.3)         | 274 (52.5)         | 274 (52.5)      | 0.79     |
| Heart disease, n (%)     | 175 (11.2)         | 66 (12.7)          | 57 (11.0)          | 52 (10.0)       | 0.38     |
| Stroke, n (%)            | 155 (9.9)          | 60 (11.5)          | 49 (9.4)           | 46 (8.8)        | 0.31     |
| CESD, mean (SD)          | 7.8 (7.8)          | 8.0 (7.7)          | 8.1 (8.2)          | 7.3 (7.6)       | 0.21     |
| APOE-4 allele positive, n (%) | 246 (15.7)  | 86 (16.5)          | 84 (16.1)          | 76 (14.6)       | 0.65     |
| MMSE, mean (SD)          | 28.5 (1.3)         | 28.3 (1.3)         | 28.7 (1.3)         | 28.7 (1.3)      | <0.01   |
| Energy intake (kcal/day) | 1167.6 (969.2−1430.2) | 935.6 (779.4−1054.1) | 1169.8 (1038.7−1319.7) | 1510.0 (1291.0−1840.8) | <0.01   |
| Calcium (mg/day) | 394.9 (312.1−501.7) | 282.7 (240.7−312.1) | 394.9 (364.7−423.0) | 569.4 (501.7−691.7) | <0.01   |
| Magnesium (mg/day) | 232.3 (187.7−289.2) | 174.2 (147.5−199.6) | 232.5 (211.4−258.3) | 321.0 (274.6−398.9) | <0.01   |
| Ca:Mg, mean (P25−P75)   | 1.69 (1.52−1.88)   | 1.59 (1.43−1.74)   | 1.70 (1.55−1.85)   | 1.91 (1.61−2.05) | <0.01   |
| Fiber (g/d) | 11.2 (8.6−15.3) | 8.3 (6.5−9.8) | 11.3 (9.6−13.5) | 16.2 (12.5−21.9) | <0.01   |
| Phosphorus (mg/day) | 892.8 (729.4−1113.3) | 687.6 (566.2−781.7) | 889.4 (796.1−1007.4) | 1230.2 (1025.8−1455.1) | <0.01   |
| Retinol (ug/d) | 591.6 (460.0−796.0) | 444.0 (370.3−524.9) | 591.7 (474.5−722.4) | 484.3 (671.3−1123.4) | <0.01   |
| Vitamin E (mg/d) | 17.7 (13.5−24.1) | 12.3 (9.6−15.23) | 17.9 (15.2−21.7) | 26.0 (20.6−34.7) | <0.01   |
| Sodium (mg/d) | 596.9 (437.4−797.7) | 430.2 (317.7−585.3) | 581.3 (461.6−732.3) | 796.0 (633.0−1045.3) | <0.01   |
| Potassium (mg/d) | 1743.4 (1387.0−2217.7) | 1265.8 (1066.2−1497.3) | 1763.3 (1549.2−1996.7) | 2479.7 (2028.2−3149.3) | <0.01   |
| Zinc (mg/d) | 9.7 (8.0−11.9) | 7.5 (6.3−8.6) | 9.7 (8.7−10.9) | 12.7 (11.0−15.6) | <0.01   |

(Continues)
### TABLE 1  
(Continued)

| Ca intake (mg/day) | Mg intake (mg/day) |
|--------------------|--------------------|
| Total              | N = 1565           |
| <339.1             | N = 521            |
| 339.1–455.8        | N = 522            |
| >455.8             | N = 522            |
| P-value for trend  |                    |

Follow-up MMSE, mean (SD)

| Follow-up time, years, mean (SD) | N = 522 | N = 522 | N = 522 |
|----------------------------------|---------|---------|---------|
| <0.01                            | 26.3 (4.7) | 27.5 (3.0) | 27.5 (2.7) |
| 0.01–0.25                        | 5.0 (1.0) | 5.3 (0.8) | 5.4 (0.8) |
| >0.25                            | 5.0 (1.0) | 5.3 (0.8) | 5.4 (0.8) |

Incident dementia, n (rate/100 person-years)

| Follow-up | N = 521 | N = 522 | N = 522 |
|-----------|---------|---------|---------|
| <0.01     | 26.3 (4.6) | 27.5 (2.7) | 27.5 (3.1) |
| 0.01–0.25 | 85 (3.3/100) | 38 (1.4/100) | 39 (1.4/100) |
| >0.25     | 85 (3.3/100) | 38 (1.4/100) | 39 (1.4/100) |

**Table 1** shows the comparison of calcium and magnesium intake with follow-up MMSE scores and incident dementia rates. Abbreviations: APOE, apolipoprotein E; Ca, calcium; Mg, magnesium; MMSE, Mini-Mental State Examination; SD, standard deviation; P25–P75, 25–75 percentile.

### TABLE 2  
Hazard ratios for the association between calcium and magnesium intake and incident dementia by Fine–Gray model

#### Calcium intake (mg/day)

| Calcium intake (mg/day) | N = 521 | N = 522 | N = 522 | P-value for trend |
|-------------------------|---------|---------|---------|------------------|
| <339.1                  | 2607.3  | 2760.8  | 2814.8  | 2589.2           |
| 339.1–455.8             | 2607.3  | 2760.8  | 2814.8  | 2589.2           |
| >455.8                  | 2607.3  | 2760.8  | 2814.8  | 2589.2           |

**Table 2** presents the hazard ratios for the association between calcium and magnesium intake and incident dementia by Fine–Gray model. The results indicate a significant association between calcium intake and reduced dementia risk. Further adjustments were made in models 2, 3, and 4, considering various covariates. Abbreviations: HR, hazard ratio; CI, confidence interval; APOE, apolipoprotein E; CESD, Center for Epidemiologic Studies Depression Scale; MMSE, Mini-Mental State Examination.
factors including dietary intake of Ca, higher intake of Mg was significantly related to a tripling of the risk for incident dementia. The highest intake tertile of Mg was associated with >2-fold increased risk for incident dementia (HR = 2.26, 95% CI: 1.02–5.00). In stratified analyses by median dietary Ca:Mg intake ratio, we found that a higher intake of Mg was significantly associated with a 4-fold increased risk for incident dementia (HR = 3.97, 95% CI: 1.29–12.25) after adjusting for all confounding factors among those with Ca:Mg intake ratios ≤1.69. In those with Ca:Mg intake ratios >1.69, higher Mg intake was not significantly related to risk for incident dementia (Table 2, Figure 2).

4 | DISCUSSION

In this population-based cohort study, we found that higher Mg intake was significantly associated with a 4-fold increased risk for incident dementia among those with baseline dietary Ca:Mg intake ratios ≤1.69. In those individuals with dietary Ca:Mg ratios >1.69, no associations were apparent. This finding was evident only in a model that adjusted for Ca intake, among other covariates.

Several previous cohort studies indicated that Ca or Mg intake may influence risk of dementia, but the results were inconsistent.²⁴⁻⁵ The Hisayama Study in Japan reported that the highest quartiles of Mg and Ca intake were associated with reduced risks of all-cause dementia (HRs [95% CI] = 0.61 [0.43–0.86]; 0.50 [0.34–0.75]; and 0.63 [0.40–1.01] for the second to the fourth quartiles, P for trend = 0.04 for Mg and 0.91 [0.64–1.28], 0.77 [0.53–1.11], 0.64 [0.41–1.00], with P for trend = 0.04 for Ca), compared to the corresponding lowest quartile.⁴ However, intake of Ca and/or Mg was not simultaneously adjusted and the potential modifying effect of Ca:Mg ratio was not considered. A cohort study in Taiwan found that patients who took MgO medication were less likely to develop dementia with a crude HR of 0.62 (95% CI: 0.45–0.86).⁵ But this study did not consider Ca and Mg intake from food and did not examine the potential interaction between these two minerals.⁵ Another cohort study in Australia showed that higher Mg intake was related to a lower risk for mild cognitive impairment (MCI; HR: 0.07, 95% CI: 0.01–0.56) or mild cognitive disorders (HR: 0.47, 95% CI: 0.22–0.99) after adjusting for potential confoundings, and this inverse association was present primarily in men.³ The Rotterdam Study examined the relationship between serum Mg levels and the risk of dementia and reported possible U-shaped curves (HR = 1.32, 95% CI: 1.02–1.70 for those with serum Mg ≤0.79 mmol/L and HR = 1.30, 95% CI: 1.02–1.67 for those with serum Mg ≥0.90 mmol/L compared to those with serum Mg between 0.80 and 0.89).⁶ The Women’s Health Initiative Memory Study demonstrated that the risks for MCI tended to be lower among participants in quintiles Q2–Q5 of Mg consumption compared to those in the lowest quintile after multivariate adjustments, including Ca. However, no significant association was observed between total Mg intake and cognitive function.³² Most of the previous studies did not address concerns of confounding by other nutrients or overall caloric intake. We took this into account by adjusting the total energy intake, dietary Ca intake (Mg model only), dietary Mg intake
(Ca model only), supplement Ca, supplement Mg, and other potential confounders in multivariate models, making it a strength of our study.

None of the previous studies considered the potential modifying effect of Ca:Mg intake ratio. Durlach proposed to maintain dietary Ca:Mg ratios close to 2.0 for optimal human health. However, this traditional advice was based on knowledgeable speculation, but not experimental evidence. Based on our studies conducted in multiple populations with different Ca:Mg intake ratios, an optimal range of Ca:Mg ratio was suggested between 1.7 and 2.6. Subsequently, we specifically designed a precision-based randomized trial to reduce Ca:Mg ratios to around 2.3 among the US population with high Ca:Mg ratios. We found optimizing Ca:Mg ratios to 2.3 optimized serum vitamin D status and significantly improved cognitive function and modified the methylation status in the APOE gene within 3 months. Among these studies were the Shanghai Men’s and Women’s Health Studies with >130,000 participants in China, in which the Ca:Mg ratio of 1.7, the median for the two cohorts, was used as the cutoff.

We found increased intakes of Ca and Mg were associated with reduced risks of total mortality and mortality due to CVD among those with Ca:Mg ratios >1.7. Specifically, high Mg intake (equal to or greater than the US Recommended Daily Allowance levels: male, 420 mg/day; female, 320 mg/day) was related to an increased risk of mortality due to CVD among those with Ca:Mg ratios ≤1.7 (HR = 1.53, 95% CI:1.08–2.16). In the current study, we found that the median for Ca:Mg intake ratios was 1.69, virtually the same as that in some previous Chinese studies. Therefore, this data-driven cutoff also has clinical meaning, arguing that Chinese populations have low ratios compared to Caucasian populations.

Further, the Shanghai Women’s and Men’s Health Studies found that the Ca:Mg ratio modified the associations between dietary intakes of Ca and Mg and risk of total mortality and mortality due to CVD. In the stratified analysis, higher intake of Mg was significantly associated with an increased risk of total mortality and mortality due to CVD only among those with dietary Ca:Mg ratios ≤1.7. In the current study, we did not find the significant association between low versus high Ca:Mg ratio and incident dementia (Table S3). We found a trend of higher intake of Ca being associated with a reduced risk of dementia among all participants, those with Ca:Mg intake ratio >1.69, or ≤1.69 only in the univariate model; however, this was not statistically significant after adjustment for covariates. This finding is partially consistent with that found in the previous study conducted in Shanghai, in which higher intake of Ca was associated with a reduced risk of total mortality, primarily among those with Ca:Mg intake ratios >1.7.

Our findings from this and previous studies indicate that Ca:Mg ratios play a critical role in modifying the effect of Ca and Mg on the risk of incident dementia as well as on CVD. These findings are biologically plausible because people with CVD are at high risk of developing dementia. Although the mechanism is not entirely clear, it is possible that in the Chinese population in Shanghai with very low Ca:Mg ratios, higher Mg intake suppresses the absorption of Ca, particularly among those with Ca:Mg intake ratios ≤1.7, which in turn, leads to Ca deficiency. This possibility was further supported by the findings from US populations with very high Ca:Mg intake ratios. In US populations, Ca:Mg intake ratios modified the associations between dietary intakes of Ca and Mg with risk of colorectal adenoma, adenoma recurrence, and colorectal cancer and also modified the effect of Ca supplementation on the risk of recurrent adenoma. These previous studies suggest that dietary Ca:Mg intake ratios between 1.7 and 2.6 may be optimal for Ca and Mg to be beneficial. In a recent precision-based randomized trial conducted in the US population with high Ca:Mg ratios, reducing Ca:Mg ratios to ≈2.3 optimized the levels of vitamin D and improved cognition and reduced methylation in the APOE gene.

There are several limitations to this study. First, dietary intakes of nutrients were only measured at baseline, but dietary intakes may change over the follow-up period. However, the study participants we followed were older adults with relatively stable dietary habits. Second, the 5-year follow-up duration was short and the events were relatively small. However, we still obtained significant findings for Mg intake overall and in those with Ca:Mg ratios ≤1.69. Third, our results may be affected by the uneven distribution of participants across territories among different strata, especially for the Ca intake–dementia association among participants with Ca:Mg ratios ≤1.69 and >1.69. Fourth, although we excluded prevalent dementia cases at baseline, there were still some people with MCI (especially of the amnestic type). We did not take any procedures to validate the self-reported FFQ in these memory-impaired individuals or promote accuracy. Fifth, we only conducted one follow-up wave for identifying incident dementia; therefore, the time element of the time-to-event analysis was very coarse. Such a coarse time scale may induce information bias of the time-to-event and affect the results from the analysis models. Sixth, the interaction between dietary Ca and Mg intakes on dementia risk may affect our results, although we did not find a significant association of dietary Ca with dementia by dietary Mg intake levels (Table S2). Seventh, the participants were elderly with good functional capacity and economic conditions; thus, our results may not be representative of the entire aging population in China. Eighth, the outcome in the current study was all-cause dementia, rather than subtypes of dementia, such as Alzheimer’s disease (AD). However, 72% of dementia in our study population was clinically diagnosed as AD. Ninth, attrition due to lost to follow-up was nearly equal to the population included in the analysis. We compared the characteristics at baseline in participants who were followed up and those lost to follow-up. As shown in Table S1, less obesity and more participants with heart diseases were found in the lost to follow-up group. Those who were followed up presented higher MMSE scores, and high intakes of total energy and various nutrients. However, Ca:Mg ratios between these two groups were not significantly different. Bias cannot be neglected because the same factors that lead to attrition (due to drop-out and death) can also cause dementia. Finally, latent/undiagnosed dementia may affect nutrition intake, for example, people forget to eat (reducing nutrition), forget they already ate and eat again (increasing nutrition), or their taste preferences or oral behaviors change (altering nutrition). Therefore, the possibility of reverse causality cannot be ruled out even though the baseline prevalent dementia cases were excluded.
In the current study conducted in a population with very low Ca:Mg ratios, high dietary intake of Mg is associated with an increased risk of dementia. Proper balance of Ca to Mg in the diet may be critical to the relationship between dietary Mg intake and risk of dementia. Guidance on how much Ca and Mg to eat in one’s daily diet may have important implications for cognitive aging and for dietary recommendations made to the public, but future studies are needed to further explore these complex relationships.

AUTHOR CONTRIBUTIONS
Qi Dai and Ding Ding conceptualized the study. Qianhua Zhao, Wanqing Wu, XiaoNiu Liang, and Zhenxu Xiao collected data. Jianfeng Luo and Chenbo Zhang undertook the data analysis. Jianfeng Luo and Chenbo Zhang drafted the manuscript. James A. Mortimer, Amy R. Borenstein, Qi Dai, and Ding Ding critically reviewed and edited the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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