Serum magnesium is associated with the risk of dementia

ABSTRACT

Objective: To determine if serum magnesium levels are associated with the risk of all-cause dementia and Alzheimer disease.

Methods: Within the prospective population-based Rotterdam Study, we measured serum magnesium levels in 9,569 participants, free from dementia at baseline (1997–2008). Participants were subsequently followed up for incident dementia, determined according to the DSM-III-R criteria, until January 1, 2015. We used Cox proportional hazard regression models to associate quintiles of serum magnesium with incident all-cause dementia. We used the third quintile as a reference group and adjusted for age, sex, Rotterdam Study cohort, educational level, cardiovascular risk factors, kidney function, comorbidities, other electrolytes, and diuretic use.

Results: Our study population had a mean age of 64.9 years and 56.6% were women. During a median follow-up of 7.8 years, 823 participants were diagnosed with all-cause dementia. Both low serum magnesium levels (<0.79 mmol/L) and high serum magnesium levels (>0.90 mmol/L) were associated with an increased risk of dementia (hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.02–1.69, and HR 1.30, 95% CI 1.02–1.67, respectively).

Conclusions: Both low and high serum magnesium levels are associated with an increased risk of all-cause dementia. Our results warrant replication in other population-based studies.

Current treatment or preventive options for dementia are limited; there is an urgent need to identify novel, potentially modifiable, risk factors. Several vascular factors are established as risk factors for dementia, as are lifestyle factors. Electrolytes have also emerged as interesting candidates, as electrolyte disturbances are associated with a variety of neurologic manifestations. In recent years, magnesium gained specific interest as low serum magnesium levels associate with an increased risk of migraine, depression, and epilepsy and potentially dementia. Most evidence for a role of magnesium in dementia comes from animal models. For instance, in both rat models for dementia as in healthy rats, magnesium was found to have a protective effect on learning. In humans, the evidence for a role of magnesium in dementia is limited and restricted to 4 case-control studies showing contrasting results, and a small randomized trial showing that a magnesium analogue improved executive functioning and working memory in participants with mild cognitive impairment. We studied the association of serum magnesium levels with the risk of dementia in a large prospective population-based cohort with long-term follow-up.

METHODS Study design, setting, and population. This study was embedded within the Rotterdam Study, a prospective population-based cohort study, ongoing since 1990 in a suburb of the city of Rotterdam, the Netherlands. The rationale and
design of this study have been described in detail elsewhere. The original cohort comprised 7,983 persons older than 55 years and living in the study area. This cohort was extended in 2000 with an additional cohort of 3,011 persons who had become 55 years or older or who had moved into the study area. In 2005, the cohort was extended again with 3,932 persons aged 45 years and older living in the research area who had not yet been included. All participants are asked to participate in follow-up examinations every 4 to 5 years.

Standard protocol approvals, registrations, and patient consents. All eligible participants provided written informed consent to participate in the study and separate consent for follow-up data collection. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Center and by the Dutch Ministry of Health, Welfare and Sport, implementing the Wet Bevolkingsonderzoek: ERGO (Population Study Act: Rotterdam Study).

Assessment of magnesium. For this study, we used blood samples collected at the third visit of the first cohort (1997–1999) and the first visits of the second (2000–2001) and the third cohort (2006–2008), as these visits are similar in design and data collection with regard to serum magnesium measurements. This time point was therefore also considered the baseline for the current analysis. Magnesium was measured in serum using a colorimetric endpoint method with a coefficient of variation (CV) for repeatability of 0.8% and a CV for intermediate precision of 1.4%–1.7%. Measurements were performed by the Department of Clinical Chemistry of the Erasmus Medical Center using a Roche/Hitachi Cobas c501 analyzer (Roche Diagnostics, Indianapolis, IN).

Ascertainment of incident dementia. The method for dementia screening and diagnosis in the Rotterdam Study has been described in more detail previously.1 In brief, participants were screened for all-cause dementia (which includes Alzheimer disease [AD], vascular dementia, and Parkinson disease dementia) using a 3-step protocol. In the first step, participants underwent a Mini-Mental State Examination (MMSE) and Geriatric Mental Schedule (GMS) at baseline and during follow-up examinations. Screen-positive participants (MMSE <26 or GMS >0) were invited for the second step, which consisted of a physician interview using the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX).3 Besides these examinations, all participants are continuously monitored for dementia using digital linkage of the study database with medical records from general practitioners in the area and the Regional Institute for Outpatient Mental Health Care. Final diagnosis is made by a consensus panel, led by a neurologist, according to the standard criteria for dementia (DSM-III-R) and AD (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association [NINCDS-ADRDA]).1 Follow-up for incident dementia was near complete (98.0% of potential person-years) until January 1, 2015.

Assessment of covariates. Body mass index was calculated as weight in kilograms divided by squared height in meters. Information on education, smoking habits, and alcohol consumption was obtained during a home interview.2 Educational level was categorized as primary education, lower or intermediate education or lower vocational education, intermediate vocational or higher general education, or higher vocational education or university. Smoking was categorized into 3 categories: nonsmoker, former smoker, and current smoker. Alcohol use was categorized into 2 categories: yes or no. Serum sodium, calcium, potassium, total cholesterol, high-density lipoprotein cholesterol, and serum creatinine were measured at the same visit as the serum magnesium levels. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation and was expressed as mL/min/1.73 m2.26 APOE genotype was determined using PCR on coded DNA samples.21–23 The assessment of diabetes mellitus, stroke, and heart failure was done through active follow-up, as described previously, using general practitioner records and hospital discharge letters.19–21 Information regarding the use of diuretics was derived from linkage to pharmacy dispensing records, as described previously.2

Statistical analyses. Means with SDs and counts with valid percentages were used to report continuous and discrete variables, respectively. We first explored the relationship between serum magnesium and incident dementia with restricted cubic splines and found it to be U-shaped (figure e-1 at Neurology.org). Therefore, to best approximate this U-shape, in all subsequent analyses we categorized serum magnesium in quintiles and used the third quintile as reference group. We used Cox proportional hazards regression models and calculated follow-up time from the date that blood was drawn until date of dementia diagnosis, death, loss to follow-up, or the end of the study, whichever came first. Participants were censored in case of death, loss to follow-up, or at the end of the study. The proportional hazard assumption was tested by plotting the log minus log survival curve and visually examining the curves, with no evidence that the assumption was violated. For all analyses we constructed 2 models. The first model was adjusted for age, sex, Rotterdam Study cohort, and educational level, whereas the second model was additionally adjusted for body mass index, systolic and diastolic blood pressure, smoking status, alcohol use, serum sodium, potassium, and calcium levels, total cholesterol/high-density lipoprotein ratio, kidney function, APOE genotype, prevalent diabetes mellitus, stroke, heart failure, and use of diuretics.

To test the robustness of our findings, we performed several sensitivity analyses. First, we excluded all cases of incident dementia within the first 4 years after serum magnesium measurement, to minimize the risk of reverse causality. Second, we excluded all participants with an estimated glomerular filtration rate below 60 mL/min/1.73 m2 to study if residual confounding by kidney function could have influenced our results. Third, we excluded all participants with prevalent diabetes, to study if the observed association is driven by the association between serum magnesium and diabetes risk. Fourth, we repeated the analysis on all-cause dementia and censored participants if they had a stroke during follow-up. Finally, we studied the effect of serum magnesium on incident AD, as this is the most common clinical subtype of dementia. Missing data on covariables (0%–4.2%) were handled by single imputation using an expectation-maximization algorithm.24 With the exception of the baseline characteristics, results are reported for imputed data. Data were analyzed using SPSS Statistics, version 21.0 (IBM, Armonk, NY), and R, version 3.1.2 (The R Foundation for Statistical Computing). We considered a 2-sided p value <0.05 as statistically significant.

RESULTS Baseline characteristics. The flowchart of our study population is shown in figure 1. Of the 11,740 eligible participants for this study, 9,883 participants had a serum magnesium measurement available at baseline. We excluded 59 participants as no informed consent was obtained to retrieve follow-up information and 255 participants were excluded due
to prevalent dementia. This resulted in a total study population of 9,569 participants. Baseline characteristics of the total study population are presented in Table 1. The mean age of the study population was 64.9 years with 56.6% being women. In our population, serum magnesium levels ranged from 0.34 to 1.17 mmol/L, with 108 participants having hypomagnesemia (defined as a serum magnesium level $<0.70$ mmol/L) and 2 participants having hypermagnesemia (defined as a serum magnesium level $>1.10$ mmol/L). Baseline characteristics per quintile of serum magnesium are presented in Table e-1. Participants within the first quintile of magnesium more often had diabetes mellitus, had a lower estimated glomerular filtration rate, and more often used diuretics. Furthermore, serum sodium and potassium levels were lower within this quintile, as compared to other quintiles.

Association between serum magnesium and incident dementia. During a median follow-up of 7.8 years (interquartile range 5.3–14.0 years), 823 participants were diagnosed with dementia, 662 of them with AD. Table 2 shows the results of the analysis on incident dementia. In the first model, we found an increased hazard for all-cause dementia (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.04–1.71) in the first quintile compared to the reference group. This association was similar in the fully adjusted model (HR 1.32, 95% CI 1.02–1.69). The fifth quintile of magnesium was also associated with a significantly increased hazard for all-cause dementia in the fully adjusted model (HR 1.30, 95% CI 1.02–1.67).

Sensitivity analysis. In Figure 2, the results of the sensitivity analyses are shown. Censoring dementia cases diagnosed in the first 4 years after serum magnesium measurement, excluding participants with declined kidney function, excluding participants with prevalent diabetes, or censoring participants for stroke yielded similar results. The association between serum magnesium and AD was similar to that of all-cause dementia, although the risk estimates did not reach statistical significance (HR 1.28, 95% CI 0.97–1.69; HR 1.21, 95% CI 0.92–1.58, respectively).

DISCUSSION In this large population-based cohort, we found that both low and high serum magnesium levels were associated with an increased risk of all-cause dementia over a median follow-up of almost 8 years. Furthermore, similar associations were found for the risk of AD.

Our findings support the results from the 2 case-control studies showing higher serum magnesium levels in patients with AD and results from 2 other
case-control studies showing lower serum magnesium levels. A previous meta-analysis concluded that these contradicting findings might be due to the use of different diagnosis criteria (either DSM or NINCDS-ADRDA), resulting in a different case definition, or the fact that the studies came from different parts of the world (either Europe/America or Asia), where ethnicity could have a modifying effect on the association. In our study, we use both criteria to diagnose all-cause dementia and AD and find that the association between serum magnesium and the risk of dementia is more likely to be U-shaped rather than linear. In addition, by using a prospective cohort design, we minimize the possibility of information bias or selection bias influencing our results. Another difference between our study and the case-control studies is the range of serum magnesium levels. In our study, serum magnesium quintiles were largely within the normal range as compared to the case-control studies, which reported on serum magnesium levels that showed overlap with the more extreme levels within our study (e.g., the first and fifth quintiles).

Table 1  Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Total population, n = 9,569</th>
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<tbody>
<tr>
<td>Age, y</td>
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<tr>
<td>Women</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<td>Diastolic blood pressure, mm Hg</td>
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<td>Educational level</td>
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<td>Primary education</td>
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<td>Lower or intermediate education or lower vocational education</td>
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<td>Intermediate vocational or higher general education</td>
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<td>Higher vocational education or university</td>
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<tr>
<td>Smoking</td>
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<td>Never</td>
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<td>Current</td>
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<tr>
<td>Alcohol use</td>
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<tr>
<td>Serum magnesium, mmol/L</td>
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<td>Serum sodium, mmol/L</td>
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<td>Serum calcium, mmol/L</td>
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<tr>
<td>Serum potassium, mmol/L</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
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<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
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<tr>
<td>Estimated glomerular filtration rate,a mL/min/1.73 m²</td>
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<tr>
<td>APOE genotype</td>
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<td>34</td>
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<td>44</td>
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<tr>
<td>History of diabetes mellitus</td>
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<td>History of stroke</td>
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<tr>
<td>History of heart failure</td>
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<tr>
<td>Use of diuretics</td>
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Values are counts (valid percentages) or means (SD). Data are shown for nonimputed data. The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.10
Our results are similar to results found in a population-based cohort study in Japan, in which higher self-reported dietary intake of magnesium was found to be associated with a decreased risk of all-cause dementia. Different from our results is that this previous study found a linear rather than a U-shaped association. A limitation of using dietary magnesium intake is that this association could also be the result of other nutrients within the diet or an overall healthier eating pattern, as foods like green leafy vegetables are often magnesium-rich. In addition, dietary magnesium intake only weakly correlates with serum magnesium levels, most likely due to the fact that magnesium absorption, from the diet into serum, strongly depends on other dietary contents and body stores of magnesium.

In the current literature, there are 2 hypotheses for the role of magnesium in dementia. One is a direct effect of neuronal magnesium on regulation of the NMDA receptor. The NMDA receptor plays an important role in learning and memory and magnesium modulates the calcium influx through this receptor, which is essential for its functioning. An important assumption within this hypothesis is the possibility of serum magnesium to influence neuronal levels of magnesium, which is still under debate. A second hypothesized pathway, through which serum magnesium can influence dementia risk, is oxidative stress. Magnesium deficiency has been found to stimulate secretion of inflammatory mediators like interleukins, tumor necrosis factor-α, and nitric oxide. These mediators are thought to stimulate atherosclerosis and thereby increase the risk of dementia.

Several limitations of our study should be noted. First, we only have a single measurement of serum magnesium. Although serum magnesium levels are relatively stable over time, we cannot rule out that changes in serum magnesium levels over time have influenced our results. Second, serum magnesium levels in our study were virtually all within the clinically defined normal range; therefore, we are unable to study the effect of hypomagnesemia. However, we expect the effect estimates of hypomagnesemia or

<table>
<thead>
<tr>
<th>Table 2 Association between serum magnesium and incident dementia</th>
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<tr>
<td>First quintile (≤0.79 mmol/L)</td>
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<td>--------------------------------</td>
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<tr>
<td>No. of participants (events)</td>
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<td>Incidence rate per 1,000 person-years (95% CI)</td>
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<td>Hazard ratio (95% CI)</td>
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<td>Model 1</td>
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<td>Model 2</td>
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Abbreviation: CI = confidence interval.
Model 1: adjusted for age, sex, Rotterdam Study cohort, and educational level. Model 2: same as model 1 and additionally adjusted for body mass index, systolic and diastolic blood pressure, smoking status, alcohol use, serum sodium, potassium and calcium levels, total/high-density lipoprotein cholesterol ratio, estimated glomerular filtration rate, APOE genotype, history of diabetes mellitus, stroke, or heart failure, and use of diuretics.

Figure 2 Sensitivity analyses
The robustness of our findings was tested using multiple sensitivity analysis. For all analyses, the full adjusted model was used. The effect estimates for all-cause dementia are the same estimates as in table 2. In the first sensitivity analysis, we censored all dementia cases occurring in the first 4 years after serum magnesium measurement. In the second analysis, we excluded all participants with an estimated glomerular filtration rate below 60 mL/min/1.73 m². In the third analysis, we excluded all participants with prevalent diabetes. In the fourth analysis, we censored all participants if they had a stroke. In the final analysis, we used Alzheimer disease as an outcome instead of all-cause dementia. All significant risk estimates are marked with an asterisk.
hypermagnesemia on dementia to be higher than our observed effect estimates. Third, serum magnesium levels do not necessarily represent total body magnesium. There can still be a magnesium deficiency if serum magnesium levels are normal; therefore, misclassification could have occurred. This misclassification, however, would have occurred in both directions, thereby attenuating our risk estimates. Finally, as we are using observational data, it is difficult to infer causality from this data. We have tried to address this by performing several sensitivity analyses, including an analysis in which we censored all dementia cases occurring in the first 4 years after serum magnesium measurement, which yielded similar results. These findings strengthen the possibility of a causal relationship. Strengths of this study include the prospective population-based design, reducing information bias, the long follow-up period, and the comprehensive assessment of dementia status. Furthermore, the detailed assessment of potential confounders and the fact that adjusting for these factors did not alter our effect estimates also strengthens the possibility of a true relationship between serum magnesium levels and dementia, rather than it being the result of other confounders or intermediates. As we are the first to study this association, our results warrant replication in other population-based studies.

AUTHOR CONTRIBUTIONS

B.C.T.K. was lead author, collected the data, performed the data analyses, and wrote the manuscript. S.L. was involved in data collection, data analysis, and report writing. F.J.W. was involved in data collection, data analysis, and report writing. M.K.I. was involved in data analysis and report writing. E.J.H. was involved in data analysis and report writing. R.Z. took part in the study design and report writing. B.H.S. took part in study design and report writing. M.A.I. was responsible for overall supervision and contributed to data analysis and report writing. All authors had access to the data, commented on the manuscript drafts, and approved the final version submitted. B.H.S. is the guarantor of this work and takes responsibility for the data, accuracy of the data analysis, and the conduct of the research.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository. Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Go to Neurology.org for full disclosures.

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REFERENCES


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Qualitative study of burnout, career satisfaction, and well-being among US neurologists in 2016 (see p. 1730)

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