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RESEARCH PAPER

Serum sodium, cognition and incident dementia in the general population

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Abstract

Background: Low serum sodium may be associated with cognitive impairment and dementia in the general population, but the data remain inconclusive. Therefore, we aimed to determine the association of low serum sodium with cognitive function and incident dementia in the general population.
Methods: Participants from a prospective population-based cohort were eligible if data on serum sodium (collected between 1997 and 2008), dementia prevalence and dementia incidence were available (follow-up until 2018). Global cognitive function was assessed with the Mini-Mental State Examination (MMSE) and the general cognitive factor (G-factor, derived from principal component analysis of individual tests). Linear regression and Cox proportional-hazards models were used to assess associations of standardised continuous and categorised low serum sodium (mean − 1.96∗SD: cut-off of 137 mmol/L) with overall cognitive function and incident dementia, respectively.
Results: In all, 8,028 participants free of dementia at baseline (mean age 63.6 years, 57% female, serum sodium 142 ± 2 mmol/L), including 217 participants with low serum sodium, were included. Cross-sectionally, continuous serum sodium and/or low serum sodium were not associated with the MMSE or G-factor. However, participants with low serum sodium performed worse on the Stroop and Purdue Pegboard tests. During a median follow-up of 10.7 years, 758 subjects developed dementia. Continuous serum sodium (hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.92;1.05) and low serum sodium (HR 1.27, 95% CI 0.90;1.79) were not associated with a higher risk of incident dementia.
Conclusion: We identified no significant associations of low serum sodium with overall cognitive functioning and risk of dementia. However, low serum sodium—including levels above the clinical cut-off for hyponatremia—was associated with impairments in selected cognitive domains including attention and psychomotor function.

Keywords: sodium, hyponatremia, cognitive function, dementia, general population, older people

Key Points

- Low serum sodium might pose a risk to cognitive health in middle-aged and older adults from the general population.
- Low serum sodium is associated with worse scores on cognitive assessments of attention and psychomotor function.
- Low serum sodium is not associated with incident dementia.

Introduction

Hyponatremia (serum sodium < 136 mmol/L) is the most common electrolyte disorder especially in older individuals [1–3], and is usually caused by an increase in vasopressin-mediated water reabsorption [4]. Acute hyponatremia (development in <48 h) can lead to severe neurological complications as a consequence of cerebral oedema because of a sudden decrease in extracellular osmolality [5, 6]. Because chronic hyponatremia develops over a longer period of time (≥48 h), brain cell volume can adapt through efflux of intracellular electrolytes and organic osmolytes such as glutamate [7], an important excitatory neurotransmitter. Subsequent changes in intra- and extracellular glutamate concentrations may affect neurotransmission processes [8], possibly leading to neurological symptoms.

Indeed, chronic hyponatremia is now recognised as a risk factor for psychomotor and neurocognitive deficits [9]. Hyponatremia has been linked to cognitive impairment in community-dwelling older men [10], hospitalised patients, [11–13] and patients with kidney failure, heart failure (HF) or liver cirrhosis [14–17]. Of note, the study conducted in community-dwelling older men found low serum sodium above the clinical cut-off for hyponatremia also to be associated with cognitive impairment and cognitive decline [10].

Furthermore, one population-based cohort study even reported a 2.4-fold increased risk of dementia in patients with hyponatremia, although using retrospective data [18]. Findings from animal studies suggest that hyponatremia may sensitise astrocytes to the damaging effects of beta amyloid [19]—a hallmark of Alzheimer's dementia [20]—and in inducing memory impairment by disrupting hippocampal long-term potentiation [21].

Findings from previous studies have limited generalizability, because they were performed in selected (patient) populations [10–17] and/or applied a retrospective or cross-sectional design [11, 13, 15, 18]. Therefore, the association of serum sodium with cognitive impairment and especially dementia in the general population remains uncertain. Yet, this information is pivotal for generating more insight in the potential risk factors of impaired cognitive health in today's ageing population. Therefore, we investigated the association of serum sodium with both cognitive function and incident dementia in a prospective population-based cohort of middle-aged and older individuals with long-term follow-up.

Methods

Setting and study population

This study was embedded in the Rotterdam Study, an ongoing prospective population-based cohort study that started in 1990 with the aim to investigate the determinants and occurrence of chronic diseases in the middle-aged and older individuals from the general population. The objectives and design of the Rotterdam Study have been described in detail previously [22]. In brief, all inhabitants of the Ommoord district in Rotterdam, the Netherlands, who were aged 45 years and older were invited to participate in the study, resulting in a total study population of 14,926 participants aged 45 years and older by the end of 2008. Follow-up examinations are periodically conducted every 3–6 years. For this study, we included participants with measurements of serum sodium available at baseline, defined as the third visit of the first cohort (RSI-3, 1997–99), the first visit of second cohort (RSII-1, 2000–01) and the first visit of the third cohort (RSIII-1, 2006–08), and with information on dementia prevalence and incidence. For the analyses with cognitive function, we only included participants who additionally had cognitive test data available. Participants were followed up from the day of the baseline serum sodium measurement to the date of dementia onset, date of death or until 1 January 2018, whichever came first. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272-159521-PG). All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Assessment of serum sodium

Serum sodium was measured during the first visits of all three cohorts and during the third visit of the first cohort. Therefore, in the first cohort, repeated measurements of serum sodium were available. Serum sodium was measured by the Department of Clinical Chemistry of the Erasmus Medical Center with ion-selective electrodes using a Roche/Hitachi Cobas 8000 ISE Analyzer (Roche Diagnostics, Indianapolis, IN, USA). The cut-offs for low and high serum sodium were defined as the mean serum sodium minus 1.96 times the SD, resulting in cut-offs of 137 and 146 mmol/L, respectively.

Assessment of cognitive function

Cognitive function was assessed using a neuropsychological test battery administered at the research centre both at baseline and during follow-up visits. Assessment methods of cognitive function have been reported in detail previously [23]. In short, the neuropsychological test battery comprised the Mini-Mental State Examination (MMSE), the Letter Digit Substitution Test (LDST), the Stroop Test (Reading, Colour naming and Interference), the Word Fluency Test (WFT), the 15-Word Learning Test (WLT; Immediate recall, Delayed recall and Recognition) and the Purdue Pegboard Test (PPB; right, left and both hands, and the sum of all three). The MMSE is a widely used 30-item test to measure global cognitive function both in research and in clinical settings. MMSE scores < 25 points may indicate cognitive impairment [24]. The LDST (recording digits next to corresponding letters) assesses information processing speed [25]. The Stroop Reading subtask (reading colour names)

measures reading speed; the Colour naming subtask (naming observed colours) measures colour naming speed; and the Interference subtask (naming the observed colours of colour names displayed in incongruous ink colour) assesses the cognitive ability to inhibit stimuli interference and captures the well-known Stroop effect [26]. The WFT (naming as many words as possible from a certain category in 1 min) is an assessment of verbal fluency [27]. The 15-WLT Immediate recall subtask (recollection of words immediately after presentation) assesses verbal learning; the Delayed recall subtask (retrieval of words 10 min after presentation) assesses retrieval abilities from verbal memory; and the Recognition subtask (recognition of words presented 10 min earlier) assesses verbal memory recognition [28]. The PPB test (placing pins in holes in 30 s with the left hand, the right hand and both hands) is a measure of dexterity and (psycho)motor skill [29]. For each cognitive test, higher scores indicate better performance, except for the Stroop test for which higher scores indicate worse performance. Therefore, the inverse of the Stroop test is included in the current study to facilitate comparison to the other cognitive tests. As a measure of global cognitive function, we calculated a general cognitive factor (G-factor) by performing a principal component analysis incorporating the LDST, the Interference subtask of the Stroop Test, the WFT, the sum-score of the PPB subtasks and the delayed recall subtask of the 15-WLT. To avoid distortion of factor weights because of strongly correlated subtasks, we selected the most informative and relevant subtasks from the multi-subtask cognitive tests [23]. The G-factor was only calculated when information on all five individual cognitive tests was available.

Ascertainment of dementia

Ascertainment methods of dementia at baseline and during follow-up have been described in detail previously [30]. Briefly, participants were screened for dementia using the MMSE and the Geriatric Mental Schedule (GMS) organic level. Those with a MMSE score below 26 or a GMS score above 0 underwent further investigation and an informant interview using the Cambridge Examination for Mental Disorders in the Elderly. Additionally, all participants from the Rotterdam Study were continuously monitored for dementia through electronic linkage of the study database with medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. Data on neuroimaging were used when required for diagnosing dementia subtype. The final dementia diagnosis was made by a consensus panel led by a neurologist, using the standard criteria for dementia (DSM-III-R) and Alzheimer's disease (NINCDS–ADRDA).

Assessment of covariates

Baseline home interviews provided information on medication use, smoking and alcohol consumption. Use of sodium altering medication was defined by using the WHO's Anatomical Therapeutic Chemical (ATC) codes and includes the use of antacids (ATC A02), diuretics (ATC C03), anti-epileptics (ATC N03) and antidepressants (ATC N06). Smoking was categorised into never, past and current smoking. Alcohol consumption was calculated in grams per day. Height and weight were measured during examinations at the research centre and body mass index (BMI) was computed by dividing weight in kilograms by squared height in metres (kg/m^2). During the same examinations, systolic and diastolic blood pressures were measured at the right brachial arterial artery using a random-zero sphygmomanometer with the participant in sitting position. The final measurement was defined as the mean of two consecutive measurements. Information on the use of anti-hypertensive drugs was obtained from the baseline home interviews and through linkage to pharmacy records. Hypertension was defined as a systolic and diastolic blood pressure exceeding 140/90 mmHg, respectively, or the use of anti-hypertensive drugs. Serum total cholesterol and creatinine were measured by the department of Clinical Chemistry of the Erasmus University Medical Center using standard laboratory techniques. The estimated glomerular filtration rate (eGFR) was calculated according to the chronic kidney disease epidemiology collaboration equation [31], using serum creatinine. Diabetes mellitus was defined as a fasting serum glucose level exceeding 7.0 mmol/L, a non-fasting serum glucose level exceeding 11.1 mmol/L (in the absence of fasting serum glucose levels), the use of blood glucose lowering medication or a previous diagnosis of the disease. HF was defined as a combination of the presence of typical symptoms and signs of HF, confirmed by objective evidence of cardiac dysfunction or a positive response to the initiated treatment, which is in accordance with the European Society of Cardiology guidelines [32, 33]. Coronary heart disease (CHD) was defined as a history of myocardial infarction or a history of a coronary revascularisation procedure [33]. Stroke was defined according to the World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms that had to last for at least 24 h or leading to death, with no apparent cause other than vascular origin [34].

Statistical analysis

A more detailed description of the statistical analysis can be found in the Supplementary Statistical Methods. Linear regression models and linear mixed models were used to analyse the associations between continuous and categorised serum sodium and the cognitive test scores at baseline and over time, respectively. Both the exposure and outcomes, except for the MMSE, were standardised. Cox proportional-hazards models were used to analyse the association of continuous and categorised serum sodium with incident dementia, and participants with prevalent dementia were excluded. All analyses were performed using three models, including adjustment for age, sex and Rotterdam Study cohort (model 1), the potential confounders BMI, smoking, alcohol use,

Table 1. Baseline characteristics of the total population

Variable	Total population (n = 8,028)	Low serum sodium (n = 217)	Normal serum sodium (n = 7,614)
Age, years	63.6 ± 9.6	69.3 ± 11.9	63.4 ± 9.5
Female sex, n (%)	4,579 (57.0)	137 (63.1)	4,326 (56.8)
BMI, kg/m^2 (n = 7,951)	27.4 ± 4.3	27.4 ± 4.8	27.4 ± 4.2
Educational level (n = 7,959)			
Primary education, n (%)	905 (11.4)	38 (17.8)	844 (11.2)
Lower/intermediate general and lower vocational education, n (%)	3,181 (40.0)	83 (38.8)	3,019 (40.0)
Higher general and intermediate vocational education, n (%)	2,324 (29.2)	57 (26.6)	2,206 (29.2)
Higher vocational education and university, n (%)	1,549 (19.5)	36 (16.8)	1,479 (19.6)
Smoking (n = 7,981)			
Current smoking, n (valid %)	1,568 (19.6)	33 (15.3)	1,494 (19.7)
Past smoking, n (valid %)	3,792 (47.5)	109 (50.7)	3,600 (47.5)
Never smoking, n (valid %)	2,621 (32.8)	73 (34.0)	2,477 (19.7)
Alcohol use, g/day (n = 6,311)	9.1 ± 11.6	8.9 ± 13.3	9.1 ± 11.6
Systolic blood pressure, mmHg (n = 7,999)	139 ± 21	143 ± 21	139 ± 21
Diastolic blood pressure, mmHg (n = 7,999)	80 ± 11	78 ± 11	80 ± 11
Hypertension, n (valid %) (n = 7,931)	4,771 (60.2)	164 (75.9)	4,486 (59.7)
Diabetes, n (%)	954 (11.9)	60 (27.6)	877 (11.5)
History of CHD, n (valid %) (n = 7,990)	488 (6.1)	17 (7.9)	461 (6.1)
History of stroke, n (%)	250 (3.1)	15 (6.9)	230 (3.0)
History of HF, n (%)	175 (2.2)	14 (6.5)	158 (2.1)
eGFR, ml/min per 1.73 m^2 (n = 7,916)	81 ± 15	77 ± 17	81 ± 15
Serum cholesterol, mmol/L (n = 7,988)	5.7 ± 1.0	5.8 ± 1.1	5.7 ± 1.0
Serum sodium, mmol/L	142 ± 2	136 ± 2	142 ± 2
130–135 mmol/L	63 (0.8)	NA	NA
<130 mmol/L	5 (0.1)	NA	NA

Data are presented as number (%), number (valid %) or mean ± SD. Values are shown for non-imputed data. For variables with missing data, valid % is given. The cut-off for low serum sodium is calculated by taking the mean minus 1.96 times the SD: ≤137 mmol/L. Normal serum sodium is defined as serum sodium between 137 and 146 mmol/L. Abbreviations: CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; n, number; NA, not applicable.

serum cholesterol, eGFR, history of HF, diabetes and hypertension (model 2) and potential confounders that could also be mediators, including a history of CHD and of stroke (model 3). Stratification by age and sex and several sensitivity analyses was performed (Supplementary Materials). To account for missing values in covariates, multiple imputation using the Multivariate Imputation by Chained Equations package in R [35] was performed (missingness for all covariates < 2%, except for alcohol use, which was 21%). Statistical significance was considered at a two-sided P-value < 0.05. Data were handled and analysed using R statistical software (R-project, Institute for Statistics and Mathematics, R Core Team (2013), Vienna, Austria, version 3.6.3).

Results

Baseline characteristics

Baseline serum sodium measurements and information on dementia were available in 8,143 participants. After excluding participants with prevalent dementia, 8,028 participants remained in the study. The mean age of the study population was 63.6 years, 57% were female and the mean serum sodium was 142 ± 2 mmol/L (Table 1). In total, 217 participants had low serum sodium (≤137 mmol/L), and 68 participants had hyponatremia (serum sodium < 136 mmol/L).

Serum sodium and cognitive function

In cross-sectional analyses, continuous serum sodium was not associated with better scores on the MMSE or the G-factor (standardised mean difference (SMD) −0.01, 95% confidence interval (CI) −0.05;0.03 for the MMSE; SMD −0.02, 95% CI −0.05;0.01 for the G-factor; model 2, Table S1). Additional adjustment for history of CHD and stroke did not substantially change the results (model 3, Table S1). After categorisation of serum sodium, no association between low serum sodium and MMSE or the G-factor was observed (Figure 1 and Table S1). Similar results were obtained when investigating the change in cognitive test scores over time (Table S2). When investigating the individual cognitive tests as outcome, higher continuous serum sodium was associated with better scores on all three subtasks of the Stroop test (Table 2). Categorically, low serum sodium was associated with worse scores on two of the three subtasks of the Stroop test and on the PPB (Table 2). Differential risks by age and sex were detected only for a subset of cognitive tests (Tables S3 and S4). In the following stratification analysis, lower continuous serum sodium was associated with better MMSE and WFT scores in participants aged < 65 years (Tables S3).

Serum sodium and incident dementia

Over a median follow-up time of 10.7 years (interquartile range 8.8–15.6 years), 758 participants developed dementia,

Table 2. Association of serum sodium and low serum sodium with individual cognitive tests

	Total *n*	SMD (95% CI) Model 1	SMD (95% CI) Model 2
Serum sodium, per SD increase			
LDST	7,551	0.02 (−0.00;0.04)	0.02 (−0.00;0.04)
Stroop test			
Reading	7,368	**0.03 (0.01;0.05)**	**0.03 (0.01;0.05)**
Colour naming	7,368	**0.04 (0.02;0.07)**	**0.04 (0.02;0.06)**
Interference	7,368	**0.04 (0.02;0.06)**	**0.03 (0.01;0.05)**
WFT	7,622	−0.01 (−0.03;0.01)	−0.01 (−0.04;0.01)
15-WLT[a]			
Immediate	3,127	−0.01 (−0.04;0.03)	−0.01 (−0.04;0.03)
Delayed	3,126	−0.02 (−0.05;0.02)	−0.02 (−0.05;0.01)
Recognition	3,137	−0.01 (−0.04;0.03)	−0.01 (−0.04;0.03)
PPB[b]			
Right	5,370	0.03 (−0.00;0.05)	0.02 (−0.01;0.05)
Left	5,364	0.01 (−0.01;0.03)	0.01 (−0.02;0.03)
Both	5,336	0.02 (−0.01;0.04)	0.01 (−0.01;0.04)
Sum	5,316	0.02 (−0.00;0.04)	0.01 (−0.01;0.04)
Low serum sodium			
LDST	192	−0.08 (−0.20;0.04)	−0.07 (−0.19;0.05)
Stroop test (inversed)			
Reading	192	−0.12 (−0.26;0.01)	−0.11 (−0.24;0.02)
Colour naming	192	**−0.17 (−0.31;−0.04)**	**−0.16 (−0.29;−0.03)**
Interference	192	**−0.21 (−0.33;−0.09)**	**−0.19 (−0.31;−0.07)**
WFT	206	−0.08 (−0.21;0.05)	−0.06 (−0.19;0.07)
15-WLT[a]			
Immediate	63	−0.00 (−0.21;0.26)	0.03(−0.21;0.26)
Delayed	63	0.04 (−0.20;0.28)	0.06 (−0.17;0.31)
Recognition	63	0.10 (−0.14;0.34)	0.11 (−0.14;0.35)
PPB[b]			
Right	103	**−0.24 (−0.42;−0.07)**	**−0.21 (−0.38;−0.04)**
Left	103	**−0.22 (−0.369;−0.04)**	**−0.19 (−0.36;−0.01)**
Both	102	**−0.22 (−0.39;−0.04)**	**−0.18 (−0.35;−0.01)**
Sum	101	**−0.23 (−0.40;−0.06)**	**−0.19 (−0.36;−0.02)**

Model 1 is adjusted for age, sex and Rotterdam Study cohort; model 2 is additionally adjusted for BMI, smoking, alcohol, serum cholesterol, eGFR, history of HF, diabetes and hypertension; serum sodium and cognitive tests are standardised. The reference level in the categorical analyses is normal serum sodium. The associations with a p-value < 0.05 are highlighted in bold. [a]Only available in Rotterdam Study cohort 3. [b]Only available in Rotterdam Study cohorts 2 and 3. Abbreviations: LDST, Letter digit substitution test; WFT, Word fluency test; WLT, Word learning test; PPB, Purdue pegboard test; SMD, standardized mean difference.

corresponding to an incidence rate of 8.3 per 1,000 person-years. Continuous serum sodium was not associated with incident dementia (hazard ratio (HR) 0.98, 95% CI 0.92;1.05, model 2, Table S1). Similar results were shown when including repeated measurements of serum sodium (Table S5). Categorically, cumulative incidences of dementia for participants with low serum sodium were not significantly different from cumulative incidences of dementia for participants with normal serum sodium (Figure 2). Furthermore, a non-significant trend between low serum sodium and an increased risk of incident dementia was identified when compared with normal serum sodium (HR 1.27, 95% CI 0.90;1.79, model 2, Figure 1 and Table S1). When excluding participants using serum sodium lowering medication, low serum sodium was significantly associated with an increased risk of incident dementia (HR 2.01, 95% CI 1.28;3.17, model 2, Table S6). Other sensitivity analyses did not substantially change our results (Table S6). No differential risks by age and sex were detected (P for interaction > 0.10 for all analyses).

Discussion

In this population-based cohort study, no statistically significant association of serum sodium with overall cognitive function and risk of incident dementia was identified.

However, low serum sodium—including levels above the clinical cut-off for hyponatremia—was significantly associated with impairments in selected cognitive domains including attention and psychomotor function.

A previous study in men aged ≥ 65 years identified significant associations of low serum sodium (based on the lowest tertile of the study population: 126–140 mmol/L) with prevalent cognitive impairment and cognitive decline [10]. These associations, however, were primarily driven by the Trail B test, which assesses visuospatial and tracking ability, rather than the MMSE, a global cognitive function measure [10]. In another population aged ≥ 60 years, higher continuous (log-transformed) serum sodium was positively associated with performance on the WLT and hyponatremic patients performed worse on the WLT and Animal Fluency Test [36]. In the Hunter Community Study,

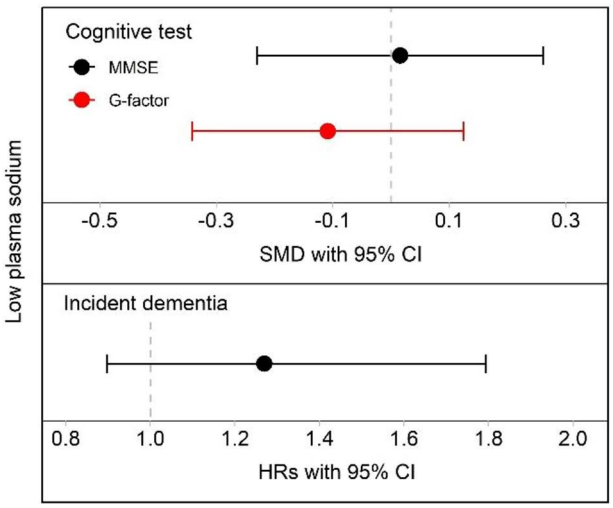

Figure 1. Association of serum sodium with global cognitive function and dementia. This figure represents the association of low serum sodium levels with the MMSE, the G-factor and incident dementia. The G-factor is standardised. The cut-off for low serum sodium is calculated by taking the mean minus 1.96 times the SD: ≤137 mmol/L. Normal serum sodium (reference category) is defined as serum sodium between 137 and 146 mmol/L. Analyses depicted in Figure A are adjusted for age, sex, Rotterdam Study cohort, BMI, smoking, alcohol, serum cholesterol, eGFR, history of HF, diabetes and hypertension.

cognition scores did not deteriorate until serum sodium dropped below 135 mmol/L [37]. In the current study, we show that low serum sodium was associated with worse scores of the Stroop and PPB tests, but not with worse overall cognitive function. Based on our data and previous studies, the general impression is therefore that lower serum sodium may affect specific domains of cognitive function, but that mainly overt hyponatremia affects overall cognitive function. Of interest, in observational studies, resolution of chronic hyponatremia independently predicted cognitive improvement [9, 12]. Intervention studies also showed that correction of chronic hyponatremia in patients can improve performance on specific cognitive tests [38–41]. Generally, previous population-based studies report that lower serum sodium is associated with lower scores on varying cognitive tests [10, 36]. Yet, in our population we observed that in participants aged < 65 years lower serum sodium was actually associated with better MMSE and WFT scores. These findings might indicate an age-dependent effect of serum sodium on cognition, but further research is needed to investigate this in more detail.

When interpreting and comparing findings from the current study and previous studies, two important aspects should be taken into account. First, assessment methods of cognitive function varied considerably amongst different studies, complicating study comparison. The different included test batteries assessed different domains of cognitive ability, but the use of combined and comprehensive measures of cognitive function such as the G-factor has been shown to adequately capture overall cognitive performance independent of the administered test batteries [42, 43]. Second, the exact threshold of serum sodium concentration that induces overall cognitive impairment remains unknown. Results from our study demonstrate that changes in selected cognitive domains can already be seen in individuals with low serum sodium above the clinical cut-offs for hyponatremia. This is reminiscent of a previous study showing that in hospitalised patients the mortality risk already increases below a serum sodium value of 138 mmol/L [44].

Regarding dementia, only one study has reported an increased risk of dementia in people with hyponatremia [18]. However, this study was retrospective and selected individuals from a health insurance database based on International Classification of Disease code for hyponatremia instead of serum sodium measurements. This approach could have led to a disproportionate inclusion of individuals with clinically relevant hyponatremia. In our study, serum sodium was not significantly associated with incident dementia, but a trend was observed with low serum sodium. Because few participants had low serum sodium, as expected in the general population, statistical power may have been insufficient to detect a significant association. Sensitivity analyses did show that low serum sodium was significantly associated with an increased risk of incident dementia in participants not using serum sodium altering medications. By excluding participants with potentially drug-induced low serum sodium, participants with low serum sodium because of underlying conditions remain. Therefore, the underlying conditions possibly explain this finding rather than the low serum sodium. However, other pathophysiological or statistical explanations cannot be fully excluded.

The main strengths of our study include the prospective design, long follow-up time, the inclusion of both individual cognitive tests and comprehensive measures of cognitive performance (G-factor) and the possibility to adjust for a wide range of potential confounders. Our study also has limitations. First, relatively few participants had hyponatremia. Therefore, our results mainly pertain to lower serum sodium, i.e. lower end of normonatremia, rather than overt hyponatremia. The limited number of participants with overt hyponatremia is to be expected in a general population. Second, repeated serum sodium measurements were limited to two measurements and only available in a subset of the population. Ideally, a larger number of repeated measurements were available to confirm the chronicity of lower serum sodium or hyponatremia and analyse fluctuations in serum sodium over time. Finally, although we adjusted for a wide range of potential confounders, residual confounding cannot be ruled out completely.

In conclusion, although no significant association of serum sodium with overall cognitive function and dementia was identified, participants with low serum sodium—including levels above the clinical cut-off for

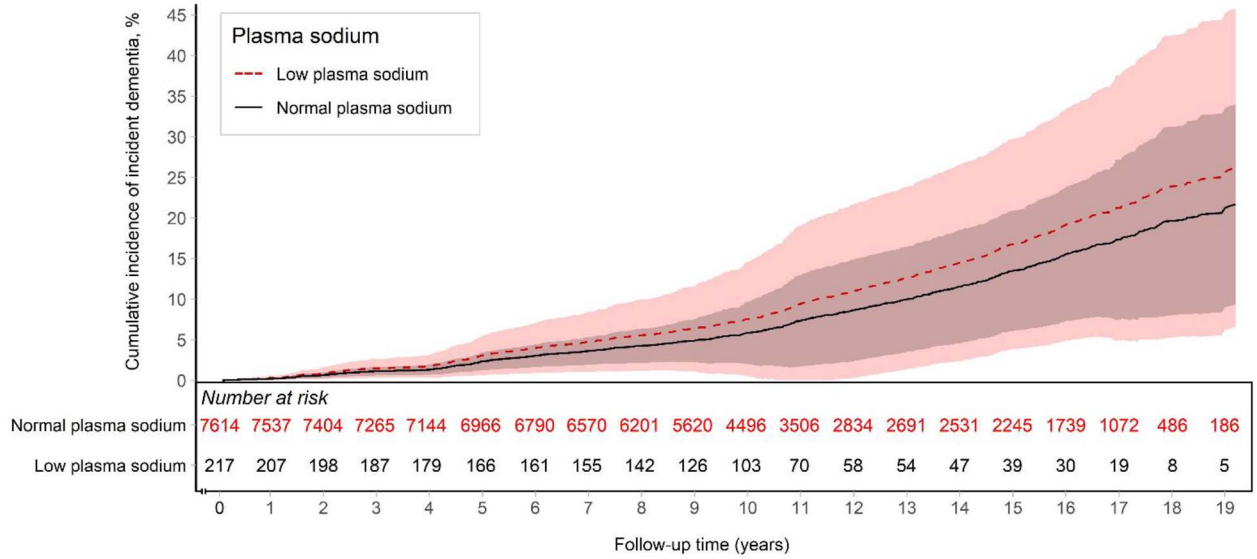

Figure 2. Cumulative incidence of incident dementia by serum sodium level. Cumulative incidences by serum sodium categories, adjusted for age and sex. The cut-off for low serum sodium is calculated by taking the mean minus 1.96 times the SD: ≤137 mmol/L. Normal serum sodium (reference category) is defined as serum sodium between 137 and 146 mmol/L.

hyponatremia—performed worse on tests of selective cognitive domains including attention and psychomotor function. Additional general population-based studies are needed to confirm our findings. Future research should also reveal whether correction of lower serum sodium improves cognition in older adults.

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Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None

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Data Availability Statement: Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

References

1. Upadhyay A, Jaber BL, Madias NE. Epidemiology of Hyponatremia. Semin Nephrol, 2009; 29: 227–38.
2. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med 2013; 126: 256–63.
3. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta 2003; 337: 169–72.
4. Spasovski G, Vanholder R, Allolio B *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant 2014; 29: i1–i39.
5. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000; 342: 1581–9.
6. Moritz ML, Ayus JC. The pathophysiology and treatment of hyponatraemic encephalopathy: an update. Nephrol Dial Transplant 2003; 18: 2486–91.
7. Verbalis JG, Gullans SR. Hyponatremia causes large sustained reductions in brain content of multiple organic osmolytes in rats. Brain Res 1991; 567: 274–82.
8. Verbalis JG. Brain volume regulation in response to changes in osmolality. Neuroscience 2010; 168: 862–70.
9. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 2006; 119: 71.e1–8.
10. Nowak KL, Yaffe K, Orwoll ES *et al.* Serum sodium and cognition in older community-dwelling men. Clin J Am Soc Nephrol 2018; 13: 366–74.

11. Brinkkoetter PT, Grundmann F, Ghassabeh PJ *et al.* Impact of resolution of hyponatremia on neurocognitive and motor performance in geriatric patients. Sci Rep 2019; 9: 1–10.
12. Suárez V, Norello D, Sen E *et al.* Impairment of neurocognitive functioning, motor performance, and mood stability in hospitalized patients with euvolemic moderate and profound hyponatremia. Am J Med 2020; 133: 986–93.e5.
13. Gosch M, Joosten-Gstrein B, Heppner H-J, Lechleitner M. Hyponatremia in geriatric inhospital patients: effects on results of a comprehensive geriatric assessment. Gerontology 2012; 58: 430–40.
14. Shavit L, Mikeladze I, Torem C, Slotki I. Mild hyponatremia is associated with functional and cognitive decline in chronic hemodialysis patients. Clin Nephrol 2014; 82: 313–9.
15. Xu R, Pi H-C, Xiong Z-Y *et al.* Hyponatremia and cognitive impairment in patients treated with peritoneal dialysis. Clin J Am Soc Nephrol 2015; 10: 1806–13.
16. Ahluwalia V, Wade JB, Thacker L *et al.* Differential impact of hyponatremia and hepatic encephalopathy on health-related quality of life and brain metabolite abnormalities in cirrhosis. J Hepatol 2013; 59: 467–73.
17. Albabtain M, Brenner MJ, Nicklas JM *et al.* Hyponatremia, cognitive function, and mobility in an outpatient heart failure population. Med Sci Monit 2016; 22: 4978–85.
18. Chung M-C, Yu T-M, Shu K-H *et al.* Hyponatremia and increased risk of dementia: a population-based retrospective cohort study. PLoS One 2017; 12: e0178977. https://doi.org/10.1371/journal.pone.0178977.
19. Gibbs ME, Gibbs CL. Deleterious effects of soluble beta amyloid on cognition, antagonism by saline and noradrenaline, a role for microglia. Neuroscience 2013; 230: 62–71.
20. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016; 8: 595–608.
21. Fujisawa H, Sugimura Y, Takagi H *et al.* Chronic hyponatremia causes neurologic and psychologic impairments. J Am Soc Nephrol 2016; 27: 766–80.
22. Ikram MA, Brusselle G, Ghanbari M *et al.* Objectives, design and main findings until 2020 from the Rotterdam study. Eur J Epidemiol 2020; 35: 483–517.
23. Hoogendam YY, Hofman A, van der Geest JN, van der Lugt A, Ikram MA. Patterns of cognitive function in aging: the Rotterdam study. Eur J Epidemiol 2014; 29: 133–40.
24. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
25. Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological Assessment. USA: Oxford University Press, 2004.
26. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop color-word test. Exp Aging Res 1993; 19: 209–24.
27. Welsh KA, Butters N, Mohs RC *et al.* The consortium to establish a registry for Alzheimer's disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994; 44: 609–14.
28. Bleecker ML, Bolla-Wilson K, Agnew J, Meyers DA. Age-related sex differences in verbal memory. J Clin Psychol 1988; 44: 403–11.
29. Tiffin J, Asher EJ. The Purdue pegboard: norms and studies of reliability and validity. J Appl Psychol 1948; 32: 234–47.
30. de Bruijn RF, Bos MJ, Portegies ML *et al.* The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam study. BMC Med 2015; 13: 132. https://doi.org/10.1186/s12916-015-0377-5.
31. Inker LA, Schmid CH, Tighiouart H *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367: 20–9.
32. Bleumink GS, Knetsch AM, Sturkenboom MC *et al.* Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure the Rotterdam study. Eur Heart J 2004; 25: 1614–9.
33. Leening MJ, Kavousi M, Heeringa J *et al.* Methods of data collection and definitions of cardiac outcomes in the Rotterdam study. Eur J Epidemiol 2012; 27: 173–85.
34. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. Eur J Epidemiol 2012; 27: 287–95. https://doi.org/10.1007/s10654-012-9673-y.
35. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw 2011; 45: 67.
36. Lee S, Min J-Y, Kim B, Ha SW, Han JH, Min KB. Serum sodium in relation to various domains of cognitive function in the elderly US population. BMC Geriatr 2021; 21: 1–8.
37. Gunathilake R, Oldmeadow C, McEvoy M *et al.* Mild hyponatremia is associated with impaired cognition and falls in community-dwelling older persons. J Am Geriatr Soc 2013; 61: 1838–9.
38. Ahluwalia V, Heuman DM, Feldman G *et al.* Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis. J Hepatol 2015; 62: 75–82.
39. Verbalis JG, Ellison H, Hobart M *et al.* Tolvaptan and neurocognitive function in mild to moderate chronic hyponatremia: a randomized trial (INSIGHT). Am J Kidney Dis 2016; 67: 893–901.
40. Refardt J, Kling B, Krausert K *et al.* Impact of chronic hyponatremia on neurocognitive and neuromuscular function. Eur J Clin Invest 2018; 48: e13022. https://doi.org/10.1111/eci.13022.
41. Bajaj JS, Heuman DM, Sterling RK *et al.* Validation of EncephalApp, smartphone-based Stroop test, for the diagnosis of covert hepatic encephalopathy. Clin Gastroenterol Hepatol 2015; 13: 1828–5.e1.
42. Johnson W, te Nijenhuis J, Bouchard TJ Jr. Still just 1 g: consistent results from five test batteries. Dermatol Int 2008; 36: 81–95.
43. Johnson W, Bouchard TJ Jr, Krueger RF, McGue M, Gottesman II. Just one g: consistent results from three test batteries. Dermatol Int 2004; 32: 95–107.
44. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. Arch Intern Med 2010; 170: 294–302.

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