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# Water intake, hydration status and 2-year changes in cognitive performance: a prospective cohort study

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## Abstract

**Background** Water intake and hydration status have been suggested to impact cognition; however, longitudinal evidence is limited and often inconsistent. This study aimed to longitudinally assess the association between hydration status and water intake based on current recommendations, with changes in cognition in an older Spanish population at high cardiovascular disease risk.

**Methods** A prospective analysis was conducted of a cohort of 1957 adults (aged 55–75) with overweight/obesity (BMI between  $\geq 27$  and  $< 40$  kg/m<sup>2</sup>) and metabolic syndrome from the PREDIMED-Plus study. Participants had completed bloodwork and validated, semiquantitative beverage and food frequency questionnaires at baseline, as well as an extensive neuropsychological battery of 8 validated tests at baseline and 2 years of follow-up. Hydration status was determined by serum osmolality calculation and categorized as  $< 295$  mmol/L (hydrated), 295–299.9 mmol/L (impending dehydration), and  $\geq 300$  mmol/L (dehydrated). Water intake was assessed as total drinking water intake and total water intake from food and beverages and according to EFSA recommendations. Global cognitive function was determined as a composite z-score summarizing individual participant results from all neuropsychological tests. Multivariable linear regression models were fitted to assess the associations between baseline hydration status and fluid intake, continuously and categorically, with 2-year changes in cognitive performance.

**Results** The mean baseline daily total water intake was  $2871 \pm 676$  mL/day ( $2889 \pm 677$  mL/day in men;  $2854 \pm 674$  mL/day in women), and 80.2% of participants met the ESFA reference values for an adequate intake. Serum osmolality (mean  $298 \pm 24$  mmol/L, range 263 to 347 mmol/L) indicated that 56% of participants were physiologically dehydrated. Lower physiological hydration status (i.e., greater serum osmolality) was associated with a greater decline in global cognitive function z-score over a 2-year period ( $\beta$ :  $-0.010$ ; 95% CI  $-0.017$  to  $-0.004$ ,  $p$ -value = 0.002). No

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significant associations were observed between water intake from beverages and/or foods with 2-year changes in global cognitive function.

**Conclusions** Reduced physiological hydration status was associated with greater reductions in global cognitive function over a 2-year period in older adults with metabolic syndrome and overweight or obesity. Future research assessing the impact of hydration on cognitive performance over a longer duration is needed.

**Trial registration** International Standard Randomized Controlled Trial Registry, ISRCTN89898870. Retrospectively registered on 24 July 2014

**Keywords** Hydration, Water, Fluids, Serum osmolarity, Serum osmolality, Cognition, Cognitive function, Cognitive performance, PREDIMED-plus

## Background

Cognitive decline is an important public health concern given 55 million people have been diagnosed with dementia and almost 80 million people are projected to be affected by 2030 [1]. Cognitive function is particularly important, especially as the population ages, because it determines the maintenance of our independence, the performance of everyday activities, and the quality of life [1]. Cognitive decline and dementia have a diverse etiology, and effective treatment is still not available [2]. For this reason, prevention strategies targeting modifiable factors, such as nutritional habits and dietary intake to slow the development of cognitive impairment, remain a promising public health approach [2]. Evidence to date assessing individual dietary factors and dietary patterns in relation to cognitive health has been summarized in the *Lancet Neurology* [3], while there is information related to various macro- and micronutrients and patterns, evidence related to water appears limited.

Water intake is a nutritional habit that is often overlooked, yet it is considered essential for the optimal physiological function of the human body [4]. As the most abundant component of the human body, water intake and optimal hydration are considered key aspects for the proper functioning of organ systems, aiding, among others, in efficient digestion, elimination of toxins, energy production, thermoregulation, and joint lubrication, as well as a multitude of biochemical reactions [5, 6]. Furthermore, proper hydration is thought to be important for optimal cognitive functioning as it plays a vital role in neural conductivity [7].

Dehydration occurs when the body loses more water than is taken in, whereas hypohydration refers to the state of water deficit; these conditions result in less-than-optimal hydration and may elicit adverse physiological consequences [8]. For the purposes of this paper, dehydration will be the term used to encompass the state of improper hydration due to unbalanced water loss or water deficit. In Europe, the percentage of the population reported to have inadequate water intake is estimated to vary from 5 to 35% [9–11]. Understanding water intake and hydration

status is of particular importance in older adults as this population tends to be less likely to meet recommendations on water intake and is at greater risk for dehydration due to blunted sensitivity to thirst signals, lower body reserves due to reduced muscle mass, reduced ability to deal with heat stress, and use of medications or laxatives with diuretic effects [12–15]. Multiple health organizations and dietary guidelines have acknowledged that adequate hydration status is associated with the preservation of physical and mental functions and that water intake is the best way to achieve hydration [16–19].

To maintain adequate hydration status, several countries and public organizations have proposed water intake recommendations for the public [20, 21]. These recommendations have been determined based on data from population studies and accounted for water from beverage and food sources [22]. For instance, the European Food Safety Authority (EFSA), based on data from population studies from 13 European countries, proposed the dietary reference values (DRV) for the adequate intake (AI) of water which increases with age up to 2.5 L and 2.0 L of water daily for men and women (aged 14 to 70 years), respectively [20]. Similarly, the Institute of Medicine (IOM) proposed increasing water intake levels with age up to 3.7 L/day and 2.7 L/day (aged 19 to 70 years) in men and women, respectively. Yet, the World Health Organization and other guidelines related to cognitive health do not currently include recommendations related to water intake or hydration status [23–25]. Further understanding of health behaviors, such as cognitive functioning, related to something as fundamental as water intake can have a substantial impact on public health.

Inadequate water intake and dehydration have been associated with existing signs of cognitive impairment among older adults living in long-term care facilities [26–29]. Moreover, acute studies have shown that dehydration and water supplementation affect mood and cognitive performance [30]. However, fluid and water intake has received limited attention in epidemiological studies, and the literature scarcely examines water intake as a predictor of

cognitive performance among older adults. The few studies that have assessed hydration status as a potential predictor of cognitive function among community-dwelling older adults have been inconclusive [31–34]. Furthermore, to date, few studies have prospectively captured and examined the impact of water and hydration status on cognitive function over a multi-year period. Therefore, the objective of the present analyses was to prospectively investigate the relation between hydration status, water intake, and 2-year changes in cognitive performance in community-dwelling older adults with metabolic syndrome and overweight or obesity.

## Methods

### Study design

This prospective cohort study is based on data collected during the first 2 years of the PREDIMED-Plus (Prevencción con Dieta MEDiterránea Plus) study. Briefly, the PREDIMED-Plus study is an ongoing randomized, parallel-group, 6-year multicenter, controlled trial designed to assess the effect of lifestyle interventions on the primary prevention of cardiovascular disease. The primary aim of the trial is to assess the effects of an intensive weight loss intervention based on an energy-reduced Mediterranean diet (MedDiet), physical activity promotion, and behavioral support (intervention group) compared to usual care and dietary counseling only with an energy-unrestricted MedDiet (control group) on the prevention of cardiovascular events. Details of the design and methods of PREDIMED-Plus have been previously described [35, 36] and are available at <https://www.predimedplus.com/>.

### Ethics, consent, and permissions

The PREDIMED-Plus study protocol and procedures were approved by the Research Ethics Committees from each of the participating centers, and the study was registered with the International Standard Randomized Controlled Trial Registry (ISRCTN; [ISRCTN89898870](https://www.isrctn.com/ISRCTN89898870)). All participants provided written informed consent.

### Study participants

PREDIMED-Plus participants were recruited from 23 centers across Spain between September 2013 and December 2016. A total of 6874 adults met the eligibility criteria and were randomly allocated in a 1:1 ratio to either the intervention or the control group. Couples sharing the same household were randomized together, and the couple was used as a unit of randomization. Eligible participants were community-dwelling adults (aged 55 to 75 for men; 60 to 75 for women) with overweight or obesity (BMI: 27 to 40 kg/m<sup>2</sup>) who met at least three criteria for metabolic syndrome (35), without previous cardiovascular events or diagnosed neurodegenerative diseases at baseline. All participants provided written informed consent.

The present longitudinal analysis involves a sub-study conducted in 10 of the 23 PREDIMED-Plus recruiting centers. Of the participants in the PREDIMED-Plus sub-study who had a completed validated 32-item Spanish fluid intake questionnaire, participants were excluded if they did not have a completed baseline Food Frequency Questionnaire (FFQ) or who reported implausible total energy intakes based on those proposed by Willet ( $\leq 500$  and  $\leq 3500$  kcal/day in women and  $\leq 800$  and  $\leq 4000$  kcal/day in men) [37]. For the water and fluid intake analyses, using the interquartile range method (using a 1.5 multiplier for the first and third quartiles), participants with extreme intakes of fluid (daily fluid intakes for men  $< 188$  mL or  $> 3862$  mL and women  $< 263$  mL or  $> 3539$  mL) were excluded for the assessment of water and fluid intakes. Similarly, participants without blood sample values for urea, sodium, potassium, glucose, and serum osmolarity values  $< 100$  mmol/L were also excluded from the analyses of hydration status and cognition. Furthermore, associations were tested for those participants who had completed the various cognitive tests.

### Assessment of water and fluid intake

A validated, semi-quantitative 32-item Beverage Intake Assessment Questionnaire (BIAQ) [10] and a 143-item validated semi-quantitative FFQ (38) specifying usual portion sizes, were administered by trained dietitians to assess habitual fluid and dietary intakes, respectively. These two questionnaires have been validated within populations of older, Spanish individuals, which are analogous to the current study population, and both have been found to be reproducible with relative validity [10, 38]. The BIAQ recorded the frequency of consumption of various beverage types during the month prior to the visit date. The average daily fluid intake from beverages was estimated from the servings of each type of beverage. The questionnaire items on beverages included: tap water, bottled water, natural fruit juices, bottled fruit juices, natural vegetable juices, bottled vegetable juices, whole milk, semi-skimmed milk, skimmed milk, drinking yogurt, milkshakes, vegetable drinks, soups, jellies and sorbets, soda, light/zero soda, espresso, coffee, tea, beer, non-alcoholic beer, wine, spirits, mixed alcoholic drinks, energy drinks, sports drinks, meal replacement shakes, and other beverages. The water and nutrient contents of the beverages were estimated mainly using the CESNID Food Composition Tables [39], complemented with data from the BEDCA Spanish Database of Food Composition [40].

The FFQ collected data on food intake based on the year prior to the visit according to nine possible frequency categories, which ranged from “never or almost never” to “ $> 6$  portions/day” and based on the dietary guidelines for the Spanish population [41]. The information collected

was converted into grams per day, multiplying portion sizes by consumption frequency and dividing the result by the period assessed. Ten food groups composed of vegetables, fruits, legumes, cereals, dairy beverages, meat and poultry, fats, nuts, fish/seafood, and other foods were determined to assess the contribution of foods to total water intake. Food groups and energy intake were estimated using Spanish food composition tables [42, 43]. Drinking water intake, water intake from all fluids, total water intake, EFSA total fluid water intake (TFWI), and EFSA total water intake (TWI) were computed (descriptions summarized in Additional file 1: Table S1). Drinking water intake was estimated based on tap and bottled water intakes based on BIAQ responses. Water intake from all fluids was computed from tap and bottled water, plus water from other beverages based on responses to the BIAQ. Total water intake encompassed water intake from all fluids in addition to water present in food sources based on responses to the FFQ. Water intake was further categorized based on established reference values. The EFSA recommendations for total water intake (EFSA TWI) for older adults (2.5 L/day and 2.0 L/day for men and women, respectively) in conditions of moderate environmental temperature and moderate physical activity [20] were used as reference values. Further categorizations were determined based on total water intake from fluids alone, based on EFSA recommendations (EFSA TFWI), where recommended levels for older adults are set to at least 2.0 L/day and 1.6 L/day for men and women, respectively [20].

#### Assessment of hydration status

Hydration status was estimated based on calculated serum osmolarity (SOSM), which is considered a more reliable biomarker of hydration status than urinary markers in older adults [44]. Fasting serum glucose, urea, sodium, and potassium were measured by standard methods. Blood urea nitrogen was determined from urea values using the conversion factor of 0.357 and reported in mmol/L. With all relevant serum analyte measures presented in mmol/L, SOSM was estimated using the following equation [45]:

$$\text{SOSM} = 1.86 * (\text{sodium} + \text{potassium}) + 1.15 * \text{glucose} + \text{blood urea nitrogen} + 14$$

Based on this equation, dehydration, impending dehydration, and hydrated statuses were defined as SOSM > 300, 295–300, and < 295 mmol/L, respectively [28, 46].

$$\text{GCF} = (Z_{\text{MMSE}} + Z_{\text{CDT}} + Z_{\text{VFT-a}} + Z_{\text{VFT-p}} + (-Z_{\text{TMT-A}}) + (-Z_{\text{TMT-B}}) + Z_{\text{DST-f}} + Z_{\text{DST-b}}) / 8$$

#### Assessment of cognitive performance

A battery of 8 neuropsychological tests assessing different cognitive domains was administered at baseline and 2-year follow-up by trained staff to assess cognitive performance. The following tests were assessed: the Mini-Mental State Examination (MMSE), two Verbal Fluency Tests (VFTs), two Digit Span Tests (DSTs) of the Wechsler Adult Intelligence Scale-III (WAIS-III), the Clock Drawing Test (CDT), and two Trail Making Tests (TMTs).

Briefly, a Spanish-validated version of the MMSE questionnaire, a commonly used cognitive screening test, was used in the present analysis [47]. A higher MMSE score indicates better cognitive performance [48]. Verbal ability and executive function were evaluated using the VFTs, which consist of two parts: the semantic verbal fluency task-animal category version (VFT-a) and the phonemic verbal fluency task-letter “p” version (VFT-p) [49]. The DST of the WAIS-III Spanish version assessed attention and memory. The DST Forward Recall (DST-f) is representative of attention and short-term memory capacity, and the DST Backward Recall (DST-b) is considered as a test of working memory capacity [50, 51]. The CDT-validated Spanish version was mainly used to evaluate visuospatial and visuo-constructive capacity [52–54]. Lastly, the TMT, another tool often used to assess executive function, consists of two parts. Part A (TMT-A) assessed attention and processing speed capacities, and part B (TMT-B) further examined cognitive flexibility [55]. All instruments included in the cognitive battery have been standardized for the Spanish population in the age range of the study population.

To assess overall cognitive function, a global cognitive function (GCF) score was determined as the main outcome measure, in addition to evaluating the individual neuropsychological tests (supplementary analyses). Raw scores at baseline and scores of changes at 2 years of follow-up for each individual cognitive assessment, as well as GCF, were standardized using the mean and standard deviation from the baseline measurements as normative data, creating z-scores [56]. GCF was calculated as a composite z-score of all 8 assessments, adding or subtracting each individual test value based on whether a higher score indicates higher or lower cognitive performance, respectively, using the formula:

### Covariate assessment

The trained staff collected baseline socio-demographic (i.e., sex, age, education level, and civil status) and lifestyle (i.e., physical activity, total energy intake, alcohol intake, caffeine consumption [57], sleeping habits, and smoking status) related variables, as well as information about medication use, in face-to-face interviews using self-reported general questionnaires and a 143-item validated semi-quantitative FFQ for the dietary related variables [38], which were further estimated using Spanish food composition tables [42, 43]. Leisure time physical activity was estimated using the validated Minnesota-REGICOR Short Physical Activity questionnaire [58]. These socio-demographic and lifestyle variables were considered as possible covariates because of reports that younger adults, women, individuals with higher educational attainment, married, more active, greater consumers, and non-smokers tend to consume higher amounts of fluids from beverages and foods and hence more likely to meet recommendations on water intake [59, 60]. Alcohol was accounted for as a potential covariate as it may act as a diuretic at certain levels [61] as well as being associated with an elevated risk of dementia when consumed regularly [62]. Similarly, caffeinated beverages may have a mild diuretic effect [63], as well as may affect attention and alertness [64] and could be associated with reduced cognitive decline and dementia risk [65]. Sleeping habits have also been associated with cognitive health [66]. Anthropometric measures, including weight and height were measured by trained staff using calibrated scales and wall-mounted stadiometers, respectively. Body mass index (BMI), which may modify the relationship between water intake and hydration status [67], was calculated as weight in kilograms divided by height in meters squared. History of chronic disease (i.e., type 2 diabetes, hypertension, and hypercholesterolemia) was self-reported or collected from patient medical records and included as these conditions may cause fluid imbalance, cause dehydration, and have been associated with cognitive performance possibly leading to mild cognitive impairment [68–70]. Depressive symptomatology was evaluated using the Beck Depression Inventory-II (BDI-II), given the association observed with cognitive health [71] where depressive symptomatology risk was established as a score  $\geq 14$  [72].

### Statistical analyses

For the present analyses, a prospective cohort study was conducted within the framework of the PREDIMED-Plus study using the database updated to December 22, 2020. Participants were categorized into quantiles based on baseline water intake (drinking water, water intake from all fluids, total water intake), recommended categories of

water intake (EFSA TWI, EFSA, TFWI), and hydration status according to serum osmolality. Baseline characteristics of participants for each category and quantile of water intake and hydration status were presented as numbers and percentages using Pearson's chi-square test for categorical variables and means  $\pm$  standard deviations or median (interquartile range [P25–P75]) using one-way ANOVA or Kruskal Wallis test for continuous variables, as appropriate.

Multivariable linear regression models were fitted to assess longitudinal associations comparing the 2-year change in cognitive function across baseline variables of hydration status and water intake and for meeting the EFSA recommendations for TWI and TFWI [20]. When analyses were performed with categorical variables,  $p$  for trend was calculated. The  $p$  for linear trend was calculated by assigning the median value of each category and modeling it as a continuous variable.

Multivariable linear regression models were adjusted for several potential confounders. Model 1 adjusted for age (years), sex (man or woman), intervention group, participating center size ( $< 100$ ,  $100$  to  $< 150$ ,  $150$  to  $< 200$ ,  $\geq 200$  participants for hydration status and  $< 100$ ,  $100$  to  $< 200$ ,  $200$  to  $< 300$ ,  $\geq 300$  participants for fluid-related analyses), respective baseline cognitive function score, and corrected for clusters (to account for couples living in the same household being randomized as a single unit). Model 2 was additionally adjusted for BMI ( $\text{kg}/\text{m}^2$ ), educational level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), smoking status (current, former, or never), and physical activity (METs/min/day). Model 3 was additionally adjusted for sleeping habits (hours of nighttime sleep), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), total energy intake (kJ per day), alcohol consumption in g/day (and adding the quadratic term), and caffeine intake (g/day). To assess the linear trend, the median value of each category of exposure variables (hydration status and various assessments of water and fluid intake) was assigned to each participant and was modeled as continuous variables in linear regression models. The Bonferroni correction was used to correct for multiple comparisons and reduce the risk of a type 1 error.

Several stratified and sensitivity analyses were additionally performed to test the robustness of the findings. First, sex-stratified regression approaches were employed to examine the relationships between hydration status and these water and fluid intake categories and 2-year changes in global cognitive function. Sensitivity analyses were additionally performed, testing the addition of estimated glomerular filtration rate (eGFR), an indicator of

renal function derived based on serum creatinine level, age, and sex [73], or dietary intake covariates (amount [g/day] of vegetables, fruits, legumes, grains, non-fluid dairy, meat, oils, fish, nuts, and pastries determined via the validated 143-item semi-quantitative FFQ [19]) to the multivariable models, but also after removal of participants with baseline MMSE < 24 (mild dementia and poorer) [74], or the removal of participants with extreme GCF z-scores at baseline (< 5% and > 95%).

The data were analyzed using the Stata 14 software program (StataCorp LP, TX, USA), and the results were originally considered statistically significant at a *p*-value (2-tailed) < 0.05, and after the Bonferroni correction, statistical significance was considered at a *p*-value (2-tailed) < 0.005.

## Results

A total of 1957 participants (mean age  $65.0 \pm 4.9$  years and 50.5% women) were available for the assessment of water and fluid intake and 1192 participants for the assessment of hydration status after excluding missing values or implausible data (Additional file 1: Fig. S1). Table 1 presents the baseline characteristics of the study population according to sex, water (tap and bottle) intake amount, and hydration status. The median (range) consumption of drinking water intake in men and women was 900 (0 to 3100) and 900 (0 to 2700) mL/day, respectively. Compared with participants in the group with the lowest drinking water intake (< 500 mL/day), those with the highest drinking water intake (1.8 to 3.1 L/day) were more likely to be younger ( $p < 0.001$ ), have a higher BMI ( $p = 0.001$ ), and have a lower alcohol intake ( $p < 0.001$ ). Compared to participants considered to be hydrated according to serum osmolarity status, participants considered to be dehydrated tended to be older ( $p = 0.008$ ), women ( $p = 0.008$ ), have type 2 diabetes ( $p < 0.001$ ), have depressive symptoms ( $p = 0.025$ ), and less likely to drink alcohol ( $p = 0.002$ ). Participants involved in the present analyses did not differ from the rest of the participants enrolled in the PREDIMED-Plus trial in terms of age, sex, BMI, and prevalence of obesity and type 2 diabetes ( $p > 0.05$  for all comparisons). Furthermore, 80% of participants (69% of men and 90% of women) met the EFSA fluid intake recommendations based on questionnaire responses, yet serum osmolarity values indicated over 50% of participants were physiologically dehydrated with only 10% of participants being considered physiologically hydrated based on serum osmolarity levels.

Figures 1 and 2 summarize the multivariable-adjusted  $\beta$ -coefficients (95% CIs) of water intake and hydration status categorically and continuously, respectively, with 2-year changes in GCF z-scores (full details from all models are presented in Additional file 1: Tables S2-S4).

Categorical analyses showed a non-significant trend towards participants considered to have a dehydrated status ( $\beta$ :  $-0.11$ ; 95% CI:  $-0.24$  to  $0.02$ ;  $p$  for trend =  $0.058$ ) to have a greater decline in global cognitive function compared to those who were considered hydrated (Fig. 1). No significant associations were observed between the various classifications of water intake (i.e., drinking water, all fluids, water from beverage and food sources, and based on EFSA water and fluid recommendations) and 2-year changes in GCF in the multivariable-adjusted models. The results of the continuous linear regression analyses suggest the presence of a significant association between hydration status and global cognitive decline over a 2-year period ( $\beta$ :  $-0.10$ ; 95% CI:  $-0.02$  to  $-0.004$ ;  $p = 0.002$ ) (Fig. 2).

Additional file 1: Tables S2-S4 show the unadjusted and multivariable-adjusted  $\beta$ -coefficients (95% CIs) of water and fluid intake (from both beverage and food sources, assessed individually and combined), as well as hydration status with changes in the global and individual assessments of cognitive function over a 2-year period. When each neuropsychological test was investigated separately, participants with the highest category of intake of drinking water (1.0 to 1.5 L/day) non-statistically significantly presented with a 0.17-point increase ( $\beta$ :  $0.17$ ; 95% CI:  $0.02$  to  $0.32$ ;  $p$  for trend =  $0.021$ ) in DST-f z-score compared to those with the lowest water intake (< 0.5 L/day) over a 2-year period (Additional file 1: Table S2). Total fluid intake showed similar findings where participants in the highest category of intake of total fluid water (2.5 L, range 2.2 to 3.4 L/day) presented with a 0.12-point increase ( $\beta$ :  $0.12$ ; 95% CI:  $0$  to  $0.24$ ;  $p$  for trend =  $0.041$ ) in DST-f z-score compared to those with the lowest water intake (1.1 L, range 0.4 to 1.4 L/day) over a 2-year period (Additional file 1: Table S2). No other associations in the multivariable-adjusted categorical or continuous analyses were observed. Furthermore, post hoc analyses of available data showed no significant differences in changes over time in the various fluid intake assessment variables (over a 2-year duration) or hydration status (over a 1-year duration) ( $p > 0.005$ ) among the participants.

## Stratified analyses

When the analyses were stratified by sex, no changes in significance were observed with the associations between water and fluid intakes, in either categorical or continuous investigations, and global cognitive function. However, when hydration-related analyses were restricted to men or women participants, findings were attenuated when women only were assessed both categorically and continuously ( $p > 0.005$ ), whereas in men those with a SOSM  $\geq 300$  mmol/L, indicating a dehydrated status, showed a higher cognitive decline over the 2-year period compared to those hydrated

**Table 1** Baseline characteristics of the participants according to sex, categories of water intake, and hydration status

Trait	Total	Women	Men	p-value	Categories of water intake			Categories of estimated SOSM <sup>a</sup>					
					Lowest	Low-moderate	High-moderate	Highest	p-value	Hydrated <sup>b</sup>	Impending dehydrated	Dehydrated	p-value
Median	900	900	900		400 ml/day	900 ml/day	1300 ml/day	1800 ml/day		292 mmol/L	298 mmol/L	304 mmol/L	
Range	(0–3100)	(0–2700)	(0–3100)		(0–500)	(800–1000)	(1071–1400)	(1800–3100)		(263–294.9)	(295–299.9)	(300–346.5)	
Frequency, n	1957	989	968		390	744	546	277		123	400	669	
<i>Socio-demographic data</i>													
Age (years)	65.0 ± 4.9	66.2 ± 4.0	63.70 ± 5.36	< 0.001	65.0 ± 4.9	65.4 ± 4.8	64.9 ± 5.0	64.0 ± 4.7	< 0.001	64.2 ± 5.0	64.3 ± 5.0	65.2 ± 4.8	0.008
Sex (women)	989 (50.5)	989 (50.5)	968 (49.5)		188 (48.2)	383 (51.5)	280 (51.3)	138 (49.8)	0.731	47 (38.2)	190 (47.5)	353 (52.8)	0.008
<i>Education level</i>													
Primary school	1023 (52.3)	629 (63.6)	394 (40.7)		188 (48.2)	399 (53.6)	297 (54.4)	139 (50.2)		68 (55.3)	211 (52.8)	372 (55.6)	
High school	545 (27.9)	235 (23.8)	310 (32.0)		111 (28.5)	201 (27.0)	148 (27.1)	85 (30.7)		29 (25.6)	112 (28.0)	184 (27.5)	
College	389 (19.9)	125 (12.6)	264 (27.3)	< 0.001	91 (23.3)	144 (19.4)	101 (18.5)	53 (19.1)	0.381	26 (21.1)	77 (19.3)	113 (16.9)	0.636
<i>Civil status</i>													
Single, divorced or separated	242 (12.4)	136 (13.8)	106 (11.0)		47 (12.1)	96 (12.9)	62 (11.4)	37 (13.4)		17 (13.8)	46 (11.5)	77 (11.5)	
Married	1513 (77.3)	684 (69.2)	829 (85.6)		300 (76.9)	560 (75.3)	423 (79.1)	221 (79.8)		97 (78.9)	319 (79.8)	520 (77.7)	
Widower	202 (10.3)	169 (17.1)	33 (3.4)	< 0.001	43 (11.0)	88 (11.8)	52 (9.5)	19 (6.9)	0.311	9 (7.3)	35 (8.8)	72 (10.8)	0.645
<i>Lifestyle factors</i>													
Body mass index, kg/m <sup>2</sup>	32.6 ± 3.5	33.0 ± 3.6	32.3 ± 3.4	< 0.001	32.3 ± 3.4	32.7 ± 3.5	32.5 ± 3.5	33.3 ± 3.5	0.001	32.3 ± 3.1	32.5 ± 3.4	32.8 ± 3.5	0.245
Physical activity (MET min/day)	348.7 ± 334.4	284.0 ± 244.6	414.8 ± 395.5	< 0.001	330.5 ± 322.4	345.2 ± 335.4	364.1 ± 348.9	352.6 ± 325.6	0.502	423.9 ± 338.2	364.5 ± 337.9	344.2 ± 346.8	0.057
<i>Smoking status</i>													
Never smoked	904 (46.2)	704 (71.2)	200 (20.7)		182 (46.7)	334 (44.9)	263 (48.17)	125 (45.1)		47 (38.2)	175 (43.8)	333 (49.8)	
Former smoker	817 (41.8)	212 (21.4)	605 (62.5)		163 (41.8)	305 (41.0)	222 (40.7)	127 (45.9)		56 (45.5)	177 (44.3)	269 (40.2)	
Current smoker	236 (12.1)	73 (7.4)	163 (16.8)	< 0.001	45 (11.5)	105 (14.1)	61 (11.2)	25 (9.0)	0.729	20 (16.3)	48 (12.0)	67 (10.0)	0.057
<i>Sleeping status, weekdays</i>													
≤ 6 h	697 (35.6)	381 (38.5)	316 (32.6)		141 (36.2)	264 (35.5)	191 (35.0)	101 (36.5)		45 (36.6)	140 (35.0)	237 (35.4)	
6 to ≤ 8 h	1096 (56.0)	517 (52.3)	579 (59.8)		215 (55.1)	412 (55.4)	315 (57.7)	154 (55.6)		65 (52.9)	227 (56.8)	366 (54.7)	
> 8 h	164 (8.4)	91 (9.2)	73 (7.5)	0.003	34 (8.7)	68 (9.1)	40 (7.3)	22 (7.9)	0.929	13 (10.6)	33 (8.3)	66 (9.9)	0.863

**Table 1** (continued)

Trait	Total	Women	Men	p-value	Categories of water intake			Categories of estimated SOSM <sup>a</sup>					
					Lowest	Low-moderate	High-moderate	Highest	p-value	Hydrated <sup>b</sup>	Impending dehydrated	Dehydrated	p-value
Sleeping status, weekends													
≤ 6 h	600 (30.7)	344 (34.9)	256 (26.5)		128 (32.9)	217 (29.3)	161 (29.5)	94 (34.2)	0.437	35 (28.5)	122 (30.7)	208 (31.1)	
6 to ≤ 8 h	1111 (56.9)	517 (52.4)	594 (61.5)		207 (53.2)	431 (58.1)	320 (58.6)	153 (55.6)		69 (56.1)	233 (58.5)	362 (54.2)	
> 8 h	241 (12.4)	125 (12.7)	116 (12.0)	< 0.001	54 (13.9)	94 (12.7)	65 (11.9)	28 (10.2)	0.437	19 (15.5)	43 (10.8)	98 (14.7)	0.371
Disease prevalence at recruitment													
Diabetes	618 (31.6)	283 (28.6)	335 (34.6)	0.004	118 (30.3)	236 (31.7)	179 (32.8)	85 (30.7)	0.851	30 (24.4)	89 (22.3)	241 (36.0)	< 0.001
Hypertension	1640 (83.8)	834 (84.3)	806 (83.3)	0.523	326 (83.6)	626 (84.1)	453 (83.0)	235 (84.8)	0.902	96 (78.1)	329 (82.3)	568 (84.9)	0.136
Hypercholesterolemia	1411 (72.1)	761 (77.0)	650 (67.2)	< 0.001	274 (72.1)	544 (73.5)	380 (71.0)	177 (70.8)	0.742	88 (71.5)	292 (73.0)	487 (72.8)	0.950
Depressive symptoms	428 (21.9)	314 (31.8)	114 (11.8)	< 0.001	94 (24.1)	154 (20.7)	116 (21.3)	64 (23.1)	0.551	20 (16.3)	81 (20.3)	171 (25.6)	<b>0.025</b>
Biochemical parameters													
Serum potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.355	4.4 ± 0.4	4.3 ± 0.4	4.28 ± 0.37	4.3 ± 0.4	<b>0.003</b>	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	<b>0.005</b>
Serum sodium (mmol/L)	139.4 ± 14.9	139.0 ± 17.1	139.9 ± 12.4	0.219	140.1 ± 12.6	139.1 ± 15.7	139.6 ± 14.5	138.8 ± 16.6	0.492	137.6 ± 2.1	140.2 ± 1.4	142.4 ± 2.1	< 0.001
Glucose (mmol/L)	6.3 ± 1.7	6.3 ± 1.6	6.4 ± 1.8	0.056	6.29 ± 1.56	6.34 ± 1.75	6.27 ± 1.64	6.43 ± 1.95	0.582	5.7 ± 0.9	6.0 ± 1.2	6.7 ± 2.0	< 0.001
Blood urea nitrogen (BUN, mmol/L)	6.6 ± 1.8	6.6 ± 1.7	6.7 ± 1.9	0.791	6.6 ± 1.7	6.7 ± 1.8	6.7 ± 1.9	6.7 ± 1.8	0.980	5.9 ± 1.5	6.1 ± 1.4	7.0 ± 1.9	< 0.001
SOSM (mmol/L) <sup>a</sup>	298.4 ± 24.4	297.6 ± 28.0	299.1 ± 20.2	0.298	299.2 ± 21.6	297.6 ± 26.6	299.3 ± 19.1	296.9 ± 31.1	0.580	292.3 ± 3.6	297.9 ± 1.4	304.1 ± 3.8	< 0.001
Dietary intake													
Alcohol intake (g/day)	9.8 ± 13.3	4.0 ± 6.7	15.7 ± 15.6	< 0.001	12.5 ± 16.2	9.8 ± 12.9	8.7 ± 12.2	8.2 ± 11.1	< 0.001	13.3 ± 16.5	11.3 ± 15.3	9.1 ± 13.2	<b>0.002</b>
Energy intake (kcal/day)	2391.7 ± 541.4	2238.3 ± 493.1	2548.6 ± 543.8	< 0.001	2422.1 ± 559.5	2391.2 ± 530.4	2374.7 ± 549.0	2384.1 ± 30.8	0.611	2400.0 ± 598.1	2342.4 ± 549.3	2365.7 ± 554.4	0.579
Caffeine intake (mg/day)	33.6 ± 31.8	29.6 ± 27.9	37.6 ± 34.9	< 0.001	38.3 ± 35.2	31.6 ± 29.7	32.6 ± 31.3	34.0 ± 32.6	0.007	35.7 ± 35.1	36.9 ± 35.3	35.8 ± 31.9	0.869



**Table 1** (continued)

Trait	Total	Women	Men	p-value	Categories of water intake			Categories of estimated SOSM <sup>a</sup>					
					Lowest	Low-moderate	High-moderate	Highest	p-value	Hydrated <sup>b</sup>	Impending dehydrated	Dehydrated	p-value
Mediterranean diet score (17-point)	8.5 ± 2.6	8.8 ± 2.6	8.1 ± 2.6	< 0.001	8.4 ± 2.6	8.3 ± 2.6	8.6 ± 2.6	8.7 ± 2.6	0.0619	8.7 ± 2.7	8.6 ± 2.6	8.6 ± 2.5	0.889
Drinking water intake (ml/day)	1031.2 ± 465.2 458.8	1033.1 ± 458.8	1029.3	0.8551	352.9 ± 123.4	892.1 ± 30.1	1300.5 ± 17.3	1829.2 ± 155.7	< 0.001	1036.0 ± 499.2	1034.7 ± 466.6	1044.3 ± 478.8	0.946
Total fluid intake (ml/day)	1842.4 ± 592.0	1797.2 ± 579.7	1888.7 ± 601.1	0.001	1232.1 ± 454.2	1691.2 ± 388.5	2103.5 ± 406.7	2593.5 ± 413.5	< 0.001	1931.1 ± 643.3	1886.5 ± 662.4	1874.4 ± 646.0	0.672
Total water intake (ml/day)	2871.1 ± 676.2	2853.5 ± 674.8	2889.2 ± 677.4	0.2434	2241.2 ± 500.9	2709.8 ± 493.7	3146.0 ± 516.0	3646.0 ± 562.8	< 0.001	2947.2 ± 710.1	2869.6 ± 743.4	2852.4 ± 735.2	0.421
Meets EFSA TWI recommendations	1569 (80.2)	898 (90.8)	671 (69.3)	< 0.001	186 (47.7)	595 (80.0)	512 (93.8)	276 (99.6)	<b>&lt; 0.001</b>	99 (80.5)	309 (77.3)	521 (77.9)	0.750
<b>Cognitive function tests</b>													
GCF <sup>c</sup>	0.04 ± 0.62	-0.15 ± 0.61	0.22 ± 0.58	< 0.001	0.10 ± 0.58	0.04 ± 0.64	-0.03 ± 0.66	0.11 ± 0.55	<b>0.018</b>	0.02 ± 0.67	0.13 ± 0.56	0.01 ± 0.64	<b>0.028</b>
MMSE	28.14 ± 1.94	27.82 ± 2.18	28.46 ± 1.60	< 0.001	28.33 ± 1.84	28.04 ± 1.98	28.02 ± 2.02	28.36 ± 1.74	<b>0.008</b>	28.23 ± 1.91	28.20 ± 2.09	28.14 ± 2.04	0.824
CDT	5.81 ± 1.31	5.68 ± 1.38	5.94 ± 1.23	< 0.001	5.83 ± 1.37	5.77 ± 1.31	5.80 ± 1.27	5.86 ± 1.31	0.767	5.75 ± 1.50	5.90 ± 1.27	5.89 ± 1.20	0.481
VFT-a	15.78 ± 4.74	14.75 ± 4.54	16.82 ± 4.71	< 0.001	16.32 ± 4.54	15.61 ± 4.98	15.49 ± 4.73	16.03 ± 4.31	<b>0.032</b>	15.77 ± 5.04	15.72 ± 4.58	15.62 ± 4.70	0.913
VFT-p	11.95 ± 4.40	11.31 ± 4.34	12.61 ± 4.36	< 0.001	12.23 ± 4.47	11.93 ± 4.49	11.65 ± 4.41	12.23 ± 3.98	0.145	11.99 ± 4.11	12.19 ± 4.35	11.46 ± 4.32	<b>0.023</b>
TMTA	55.17 ± 31.40	61.62 ± 32.56	48.94 ± 28.88	< 0.001	53.73 ± 28.75	57.04 ± 33.21	55.77 ± 32.55	51.02 ± 27.04	<b>0.037</b>	56.72 ± 28.45	54.97 ± 30.33	57.56 ± 36.13	0.474
TMTB	136.9 ± 78.4	156.6 ± 82.5	116.8 ± 68.3	< 0.001	129.9 ± 75.4	138.0 ± 79.2	142.9 ± 81.4	132.2 ± 72.6	0.06	153.2 ± 92.3	139.6 ± 81.0	146.4 ± 82.4	0.217
DST-f	8.66 ± 2.46	8.13 ± 2.32	9.19 ± 2.48	< 0.001	8.61 ± 2.33	8.74 ± 2.48	8.50 ± 2.57	8.86 ± 2.34	0.23	8.26 ± 2.62	8.74 ± 2.44	8.73 ± 2.53	0.176
DST-b	5.06 ± 2.20	4.53 ± 1.97	5.58 ± 2.28	< 0.001	5.04 ± 2.25	5.15 ± 2.15	4.85 ± 2.20	5.27 ± 2.19	0.049	4.89 ± 2.30	5.11 ± 2.11	5.02 ± 2.16	0.638

Data are n (%) or mean ± SD for categorical and quantitative variables, respectively. The exception is the diet score is represented as mean (range)

Chi-squared is used for categorical variables, and one-way ANOVA for quantitative variables

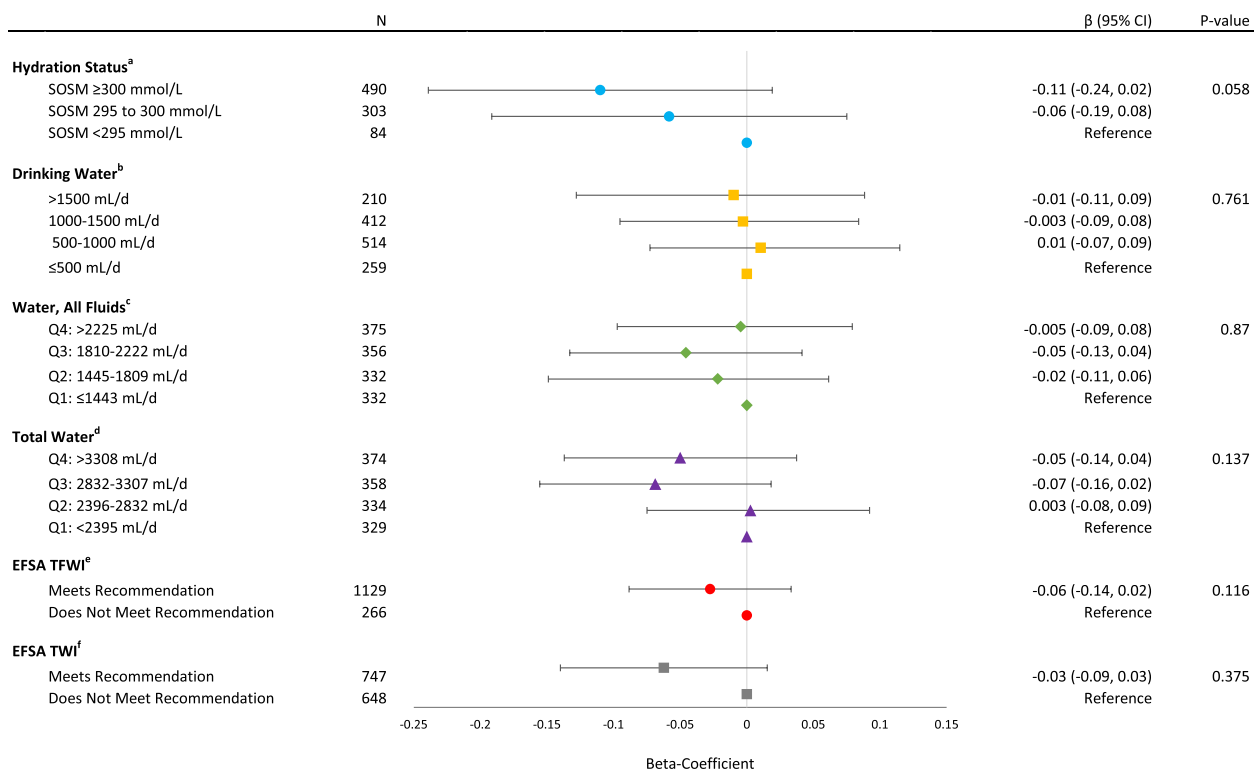
SOSM > 300 mmol/L represented a dehydrated state, 295 to 300 mmol/L represented a state of impending dehydration, and < 294 mmol/L represented a hydrated state

Abbreviations: CDT, Clock Drawing Test; DASH, Dietary Approaches to Stop Hypertension; DST-f, Digit Span Test Forward; DST-b, Digit Span Test Backward; GCF, global cognitive function; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-g, Verbal Fluency tasks semantic; VFT-p, Verbal Fluency Tasks Phonological

<sup>a</sup> SOSM represents calculated serum osmolarity and was calculated using the formula  $SOSM = 1.86 \times (Na + K) + 1.15 \times \text{glucose} + BUN + 14$ , where all analytes are in mmol/L

<sup>b</sup> Hydrated includes participants considered to be hydrated (SOSM 285 to < 295 mmol/L) and overhydrated (SOSM < 285 mmol/L). These groups were combined due to the small number of participants (n = 3) considered to be overhydrated. Assessment with the removal of these participants did not modify the findings

<sup>c</sup> GCF was calculated using the formula  $GCF = (Z_{MMSE} + Z_{CDT} + Z_{VFT-a} + Z_{VFT-p} + Z_{TMT-A}) + (-Z_{TMT-B}) + Z_{DST-f} + Z_{DST-b} / 8$



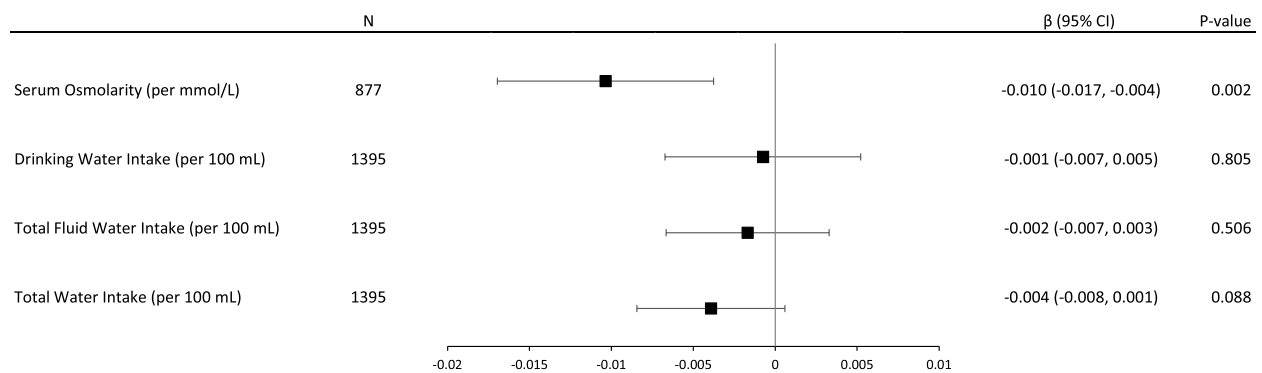
**Fig. 1** Hydration status, water and fluid intakes categorically with 2-year changes in global cognitive function (z-scores). Data are presented as beta-coefficients and 95% CI. Multivariable linear regression models were adjusted for baseline covariates, including baseline GCF score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center (for hydration status: ≤ 100, 100 to < 150, 150 to < 200, > 200 participants; for fluid-related exposures: ≤ 100, 100 to < 200, 200 to < 300, > 300 participants), body mass index (kg/m<sup>2</sup>), educational level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), physical activity (METs/min/day), sleep status (hours per day), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), energy intake (kcal/day), alcohol consumption in g/day (and adding the quadratic term), and caffeine intake (mg/day). <sup>a</sup>Hydration status refers to serum osmolality, where dehydration, impending dehydration, and hydrated statuses were defined as SOSM > 300, 295–300, and < 295 mmol/L, respectively. <sup>b</sup>Drinking water refers to tap and bottled water intakes. <sup>c</sup>Water, all fluids refers to tap and bottled water, plus water from other beverages and fluid food sources, such as soups and smoothies. <sup>d</sup>Total water refers to water from all fluids in addition to water present in food sources. <sup>e</sup>EFSA TFWI refers to the recommended levels of total fluid water intake for older adults at 2.0 L/day and 1.6 L/day for men and women, respectively. <sup>f</sup>EFSA TWI refers to the recommended levels of total water intake, from fluids and foods, for older adults at 2.5 L/day and 2.0 L/day for men and women, respectively. *Abbreviations:* EFSA, European Food Safety Authority; TFWI, total fluid water intake; TWI, total water intake; SOSM, serum osmolality

(β: -0.20, 95% CI: -0.36 to -0.04, p = 0.012 and p-trend = 0.002), and the significance remained in the continuous analyses (β: -0.013, 95% CI: -0.022 to -0.004, p = 0.004) (Additional file 1: Figs. S2-S3).

**Sensitivity analyses**

Regarding the sensitivity analyses, associations additionally adjusted for eGFR did not significantly modify the findings (Additional file 1: Tables S5-S7). Moreover, associations additionally adjusted for intake of dietary variables, where applicable, including the amount (g/day) of vegetables, fruits, legumes, grains, non-fluid dairy, meat, oils, fish, nuts, and pastries did not

significantly modify the findings (Additional file 1: Tables S5-S7). Furthermore, the main results did not substantially change after the removal of extreme GCF baseline z-scores (< 5% and > 95%). Whereas following the removal of participants with a baseline MMSE score < 24 (n = 51), the categorical association of hydration status with GCF became greater showing a more dehydrated status related to greater 2-year global cognitive decline compared to hydrated participants (p-trend = 0.046), and the association of the continuous variables remained significant (p = 0.002). The findings related to water and fluid intake did not substantially change with the removal of participants with a baseline MMSE score < 24 (Additional file 1: Tables S5-S7).



**Fig. 2** Hydration status, water and fluid intakes continuously with 2-year changes in global cognitive function (z-scores). Data are presented as beta-coefficients and 95% CI. Multivariable linear regression models were adjusted for baseline covariates, including baseline GCF score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center ( $\leq 100$ ,  $100 < 150$ ,  $150 < 200$ ,  $> 200$  participants), body mass index ( $\text{kg}/\text{m}^2$ ), educational level (primary, secondary, or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), physical activity (METs/min/day), sleep status (hours per day), depressive symptomatology (yes/no), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), energy intake (kcal/day), alcohol consumption in grams/day (and adding the quadratic term), and caffeine intake (mg/day). Beta represents the changes in global cognitive function, expressed as z-scores, with each hydration or fluid intake component continuously. Bonferroni correction analyses have been run to correct for multiple comparisons and indicate a  $p < 0.005$  is statistically significant

## Discussion

To the best of our knowledge, this is the first multi-year prospective cohort study to assess the association between water intake (from fluid and food sources) and hydration status, with subsequent changes in cognitive performance in older Spanish adults with metabolic syndrome and overweight or obesity. In this large sample of older Spanish adults, poorer hydration status was associated with greater global cognitive decline over a 2-year period, particularly in men, whereas water intake, from fluid and/or food sources, and meeting related EFSA recommendations, was not associated with global cognitive function. Nonetheless, when results of cognitive function tests were considered independently, water intake ( $> 1.5$  L/day compared to  $< 0.5$  L/day from tap or bottled water and 2.2 to 4.4 L/day compared to  $< 1.4$  L/day of water from all fluid sources) was related to better attention and short-term memory, as assessed by DST-f, over a 2-year period.

Despite the general acknowledgment that an appropriate level of fluid intake and hydration status is important for health, there have been limited investigations to date assessing the relationship between fluid intake or hydration status and cognitive function. Existing evidence suggests that good hydration status may be associated with better cognitive test results and that mild, induced dehydration can impair cognitive abilities [75], but findings are not consistent and there are only a few studies exploring the relationship of hydration status and hardly any assessing amount of water intake, with cognitive performance in older community-dwelling adults.

Of the few relevant and recent studies that have been conducted, one cross-sectional analysis of 2506 community-dwelling older American adults (aged  $\geq 60$  years) from the Nutrition and Health Examination Survey (NHANES) 2011–2014 cycles assessed both hydration status and water intake in relation to cognitive performance [34]. In comparison with the present findings, this study found women (but not men) considered to be hydrated, based on a SOSM level between 285 and 289 mmol/L, had better attention and processing speeds, based on a Digit Symbol Substitution test (DSST), than women not at optimal hydration [34]. These cross-sectional findings differ from the present observations where global cognitive function, but not individual tests related to attention and processing, was associated with hydration status. Whereas, correspondingly, water intake (but not hydration status) was positively associated with DST-f, which is similar to the DSST in that it is an indicator of attention as well as short-term memory capacity, and this was seen across all older adults (both men and women). Additionally, in the NHANES study, cognitive test scores were significantly lower among adults who failed to meet EFSA recommendations on adequate intake (AI) of water in bivariate analyses, yet this significance was attenuated in the multivariable analyses among both women and men. Yet, using the alternative AI of daily water intake of 1500 mL or more, which is comparable to the highest drinking water intake group in the present study, women scored higher on the Animal Fluency Test, a measure of verbal fluency and hence executive function, and DSST

than women with intake levels below this amount, and findings among men trended in the same direction [34].

Similarly, hydration status has been associated with cognitive function in two cross-sectional studies of older community-dwelling adults by Suhr and colleagues [32, 33]. First, Suhr et al. showed that in 28 healthy community-dwelling older adults (aged 50 to 82 years), a lower hydration status, determined in this study via total body water measured using the bioelectrical impedance method, was related to a decreased psychomotor processing speed, poorer attention, and memory [33]. A second cross-sectional study by Suhr et al. [32] conducted in 21 postmenopausal women (aged 50 to 78 years) reported a positive association between total body water, also measured by the bioelectrical impedance method, and working memory or memory skills.

Moreover, the possible relation between hydration and cognitive function shown by the present findings and demonstrated by the abovementioned cross-sectional studies in older adults align with acute heat- and exercise-induced dehydration studies in younger populations, as illustrated by a meta-analysis of 33 trials (pre-post or crossover design) of 413 adults free of disease (aged < 45 years). It should be noted that these studies assessed dehydration over a period of less than 72 h with 27 (81%) of the studies including only men participants, and 25 (76%) studies involving recreationally or highly athletic individuals. The authors concluded that despite variability among the included studies, dehydration impaired cognitive performance, particularly for tasks involving attention, executive function, and motor coordination when water deficits exceeded 2% body mass loss [76].

Conversely, a cross-sectional study conducted in Poland among 60 community-dwelling older adults (aged 60 to 93 years) found no significant relationship between cognitive performance, as assessed using the MMSE, TMT, and the Babcock Story Recall Test, and hydration status as assessed by urine specific gravity [31]. The discrepancy between the findings from this cross-sectional study and the present PREDIMED-Plus analyses might be because all participants in the cross-sectional study from Poland were considered to be adequately hydrated and hence the authors of that study could not assess the impact of a dehydrated state on cognition.

A noteworthy consideration when interpreting the literature and the main findings of the current study for practical use and in the determination of potential mechanisms of action is the distinction between water intake and water balance (related to hydration status) within the body. When homeostasis of fluids within the body is disrupted, modifying water intake may impact cognitive function, yet due to the dynamic complexity of body water regulation impacting hydration status may be

dependent on individualized physiological water intake needs [8]. Thus, while the biological mechanism by which water intake and a hydrated status may reduce the risk of cognitive decline is unclear, evidence suggests that aspects related to hydration and fluid homeostasis or a lack thereof, such as hormone regulation and changes in brain structure, could be a key underlying factor.

Several mechanisms regulate water intake and output to maintain serum osmolarity, and hence hydration status, within a narrow range. Elevated blood osmolarity resulting in the secretion of antidiuretic hormone (ADH), also known as vasopressin or arginine vasopressin, a peptide hormone which acts primarily in the kidneys to increase water reabsorption, is one such mechanism that works to return osmolarity to baseline and preserve fluid balance [77]. In addition to its role in mediating the physiological functions related to water reabsorption and homeostasis, evidence has suggested that ADH participates in cognitive functioning [78] and that the associated cognitive modulations may further interplay with sex hormones [79]. Antidiuretic hormone may be influenced by the androgen sex hormone, which is generally more abundant in the brains of males than in females [80]. As a result, the impact of ADH on cognition could be greater in males [80].

Exercise- and heat-induced acute dehydration studies implicate possible modifications to the brain structure as another potential mechanism of action for an association between water intake, hydration status, and cognitive function. Evidence has proposed that acute dehydration can lead to a reduction in brain volume and subtle regional changes in brain morphology such as ventricular expansion, effects that may be reversed following acute rehydration [81, 82]. Acute dehydration studies have further implicated hydration status in affecting cerebral hemodynamics and metabolism resulting in declines in cerebral blood flow and oxygen supply [83, 84]. A lower vascular and neuronal oxygenation could potentially compromise the cerebral metabolic rate for oxygen, thereby contributing to reductions in cognitive performance [81, 85–88]. Nonetheless, other potential unknown mechanisms cannot be disregarded.

There are several limitations and strengths of the present analyses that need to be acknowledged. The first notable limitation is that the results may not be generalizable to other populations since the participants are older Spanish individuals with metabolic syndrome and overweight or obesity. Second, measurement error and recall bias are possibilities given the use of questionnaires to estimate water and fluid intake and that these rely on responders' memory which is a component of cognitive function. However, these questionnaires have been validated and determined as reliable methods of assessing

long-term intake in the present study population [37, 38]. Third, despite its longitudinal design, water and fluid intake and hydration status were only considered at baseline; however, as the questionnaires measure habitual beverage and food intake, and older adults are considered to have reasonably stable dietary habits [37, 38], this is not expected to significantly impact the findings. Along these lines, the possible effect of seasonality on water intake and osmolarity was not considered a concern in the present analyses as the validation of the fluid questionnaire measurements included assessments at various points throughout the year (baseline vs. 6 months vs 1 year) with no significant differences observed in fluid consumption across the different time points assessed [10]. Hence, the finding of no difference between 6-month intervals, suggests no significant differences between opposing seasons (e.g., winter vs. summer; spring vs. fall). Furthermore, SOSM determination may not necessarily detect acute dehydration or rehydration immediately prior to the cognitive testing, and it is unknown whether observed elevated SOSMs were due to inadequate water intake, ADH abnormality, or other factors. While it is possible that the hydration status of some individuals was misclassified because serum osmolarity was estimated as opposed to being directly measured, the equation has been shown to predict directly measured serum osmolarity well in older adult men and women with and without diabetes or renal issues with a good diagnostic accuracy of dehydration and has been considered a gold standard for the identification of impending and current water-loss dehydration in older adults [44, 45, 89–91]. Lastly, a discrepancy was observed between the percentage of individuals that were considered to have met EFSA fluid intake recommendations and those considered to be dehydrated based on calculated osmolarity. This may have been due to the fact that the EFSA fluid intake recommendations are meant for individuals in good health [20]; whereas the present study population had overweight or obesity, and it has been shown that individuals with higher BMIs have higher water needs related to metabolic rate, body surface area, body weight, and water turnover rates related to higher energy requirements, greater food consumption, and higher metabolic production [92]. Strengths of the present analyses include the longitudinal, prospective design, the large sample size, the use of an extensive cognitive test battery, the use of validated questionnaires, and the robustness of the current findings due to the adjustment of relevant covariates.

## Conclusions

Findings suggest that hydration status, specifically poorer hydration status, may be associated with a greater decline in global cognitive function in older

adults with metabolic syndrome and overweight or obesity, particularly in men. Further prospective cohort studies and randomized clinical trials are required to confirm these results and to better understand the link between water and fluid intake, hydration status, and changes in cognitive performance to provide guidance for guidelines and public health.

## Abbreviations

ADH	Antidiuretic hormone
AI	Adequate intake
BDHI	Beck Depression Inventory-II
BEDCA	Base de Datos Española de Composición de Alimentos
BIAQ	Beverage Intake Assessment Questionnaire
BMI	Body mass index
CESNID	El Centro de Enseñanza Superior de Nutrición y Dietética
CDT	Clock Drawing Test
CI	Confidence interval
DRV	Dietary reference value
DSST	Digit Symbol Substitution Test
DST-b	DST Backward Recall
DST-f	DST Forward Recall
EFSA	European Food Safety Authority
eGFR	Estimated glomerular filtration rate
En	Energy
FFQ	Food Frequency Questionnaire
GCF	Global cognitive function
IOM	Institute of Medicine
ISRCTN	International Standard Randomized Controlled Trial Registry
MedDiet	Mediterranean diet
METs	Metabolic equivalents
MMSE	Mini-Mental State Examination
NHANES	Nutrition and Health Examination Survey
PREDIMED	PREVención con Dieta MEDiterránea
Q	Quartile
SOSM	Serum osmolarity
TFWI	Total fluid water intake
TMT-A	Trail Making Test Section A
TMT-B	Trail Making Test Section B
TWI	Total water intake
VFT-a	Verbal Fluency Test Animals Category
VFT-p	Verbal Fluency Test Letter “p” Category
WAIS-III	Wechsler Adult Intelligence Scale-III

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-023-02771-4>.

**Additional file 1: Table S1.** Hydration and water intake definitions. **Table S2.** Associations between cognitive assessments and water and fluid intake exposures. **Table S3.** Associations between cognitive assessments and EFSA fluid intake related guidelines. **Table S4.** Associations between cognitive assessments and hydration status. **Table S5.** Sensitivity analysis in global cognitive function according to water and fluid intake related exposures **Table S6.** Sensitivity analysis in global cognitive function according to EFSA fluid intake related guidelines. **Table S7.** Sensitivity analysis in global cognitive function according to hydration status. **Fig. S1.** Flow diagram of participants. **Fig. S2.** Continuous sensitivity analysis by sex. **Fig. S3.** Categorical sensitivity analysis by sex.

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#### Authors' contributions

LSM, JV, MF, DC, XP, ABC, JAT, JAM, and JSS contributed to the study concept and design and data extraction from the participants from the PREDIMED-Plus study which provides the framework for the present prospective cohort analysis. SKN, NB, IPG, CGM, and JSS made substantial contributions to the conception of the present study. SKN performed the statistical analyses and initial interpretation of the data. NB, IPG, CGM, and JSS contributed to the review of the statistical analyses and interpretation of the data. SKN drafted the manuscript. All authors substantively reviewed the manuscript for important intellectual content and approved the final version to be published. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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#### Availability of data and materials

The dataset supporting the conclusions of this article is available upon request pending application and approval of the PREDIMED-Plus Steering Committee. There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: [jordi.salas@urv.cat](mailto:jordi.salas@urv.cat). The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

## Declarations

#### Ethics approval and consent to participate

The PREDIMED-Plus study protocol and procedures were approved by the Research Ethics Committees from each of the participating centers, and the study was registered with the International Standard Randomized Controlled Trial registry (ISRCTN; [ISRCTN89898870](https://www.isrctn.com/ISRCTN89898870)). All participants provided written informed consent.

#### Consent for publication

Not applicable.

#### Competing interests

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