

Hydration status, water intake and changes in cognitive performance in older adults:

A prospective cohort

ADDITIONAL FILE 1

Table of Contents

TABLES	2
Supplemental Table 1. Description of the hydration and water intake exposures assessed.	2
Supplemental Table 2. Multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in cognitive performance according to water and fluid intake related exposures in the PREDIMED-Plus cohort.	3
Supplemental Table 3. Multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in cognitive performance according to EFSA fluid intake related guidelines in the PREDIMED-Plus cohort.....	11
Supplemental Table 4. Multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in cognitive performance according to hydration status in the PREDIMED-Plus cohort.	14
Supplemental Table 5. Sensitivity analysis of the multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in global cognitive function (GCF ^a , n=1395) according to water and fluid intake related exposures in the PREDIMED-Plus cohort.	17
Supplemental Table 6. Sensitivity analysis of the multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in global cognitive function (GCF ^a , n=1395) according to EFSA fluid intake related guidelines in the PREDIMED-Plus cohort.	19
Supplemental Table 7. Sensitivity analysis of the multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in global cognitive function (GCF ^a) according to hydration status in the PREDIMED-Plus cohort.....	20
FIGURES	22
Figure 1. Flow diagram of participants in the PREDIMED-Plus sub-study for the analysis of a priori water intake and hydration status and cognitive performance in the PREDIMED-Plus trial.	22
Figure 2. Beta-coefficients and 95% CI for hydration status and water and fluid intakes continuously with 2-year changes in global cognitive function (z-scores) in women (A) and men (B).....	23
Figure 3. Beta-coefficients and 95% CI for hydration status and water and fluid intakes categorically with 2-year changes in global cognitive function (z-scores) in women (A) and men (B).....	24

TABLES

Supplemental Table 1. Description of the hydration and water intake exposures assessed.

Exposure	Definition
Dehydration Status	Estimated based on calculated SOSM using fasting serum glucose, blood urea nitrogen, sodium, and potassium levels according to the equation: $\text{SOSM} = 1.86 * (\text{sodium} + \text{potassium}) + 1.15 * \text{glucose} + \text{blood urea nitrogen} + 14$ <i>Dehydrated</i> was considered SOSM > 300 mmol/L <i>Impending dehydration</i> was considered SOSM 295 to 300 mmol/L <i>Hydrated</i> was considered < 295 mmol/L
Water Intake	Tap and bottled water use based on responses to the 32-item BIAQ.
Water, All Fluids	Tap and bottled water, plus water from other beverages and liquid food sources (e.g., soups) based on responses to the 32-item BIAQ.
Total Water	Water from foods based on responses to the 143-item FFQ (e.g., fruits, vegetables) plus drinking water and other beverage-related sources based on responses to the 32-item BIAQ.
EFSA TFWI	Meets recommendations for total water intake from fluids based on data from responses to the 32-item BIAQ, according to EFSA regulations and guidance¹. Does Not Meet EFSA TFWI = Men: < 2000 ml/d; Women < 1600 ml/d AND Does Meet EFSA TFWI = Men ≥ 2000 ml/d; Women ≥ 1600 ml/d
EFSA TWI	Meets recommendations for total water intake (fluid + food sources), according to EFSA regulations and guidance¹. Water intake amounts were based on responses to the 32-item BIAQ and 143-item FFQ. Does Not Meet EFSA TWI = Men: < 2500 ml/d; Women < 2000 ml/d AND Does Meet EFSA TWI = Men ≥ 2500 ml/d; Women ≥ 2000 ml/d

Abbreviations: BIAQ, Beverage Intake Assessment Questionnaire; EFSA, European Food Safety Authority; FFQ, Food Frequency Questionnaire; d, day; SOSM, serum osmolality; TFWI, total fluid water intake; TWI, total water intake.

¹EFSA Panel on Dietetic Products Nutrition and Allergies (NDA). Scientific Opinion on Dietary Reference Values for water. EFSA Journal. 2010;8(3):1459–507.

Supplemental Table 2. Multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in cognitive performance according to water and fluid intake related exposures in the PREDIMED-Plus cohort.

WATER INTAKE (BEVERAGE) ^a											
Intake Range (ml/day)	N	Categorical				Continuous ^b					
		<500 β (95% CI)	500 to 1000 β (95% CI)	1000 to 1500 β (95% CI)	>1500 β (95% CI)	p for trend	β (95% CI)		p-value		
GCF^c	1395										
crude model		Reference	-0.07 (-0.22, 0.07)	-0.14 (-0.30, 0.01)	0.04 (-0.13, 0.21)	0.883	-0.00001	(-0.00011, 0.00010)	0.898		
model 1		Reference	-0.01 (-0.09, 0.07)	-0.01 (-0.10, 0.08)	-0.02 (-0.12, 0.08)	0.750	-0.00001	(-0.00007, 0.00005)	0.850		
model 2		Reference	0.01 (-0.08, 0.09)	-0.01 (-0.09, 0.08)	-0.02 (-0.11, 0.08)	0.669	-0.00001	(-0.00007, 0.00005)	0.716		
model 3		Reference	0.01 (-0.07, 0.09)	0.00 (-0.09, 0.08)	-0.01 (-0.11, 0.09)	0.761	-0.00001	(-0.00007, 0.00005)	0.805		
MMSE	1651										
crude model		Reference	-0.02 (-0.15, 0.10)	-0.02 (-0.15, 0.11)	0.13 (-0.02, 0.28)	0.154	0.00006	(-0.00004, 0.00016)	0.229		
model 1		Reference	-0.01 (-0.12, 0.10)	0.00 (-0.11, 0.11)	0.07 (-0.06, 0.20)	0.333	0.00003	(-0.00005, 0.00012)	0.469		
model 2		Reference	-0.01 (-0.12, 0.09)	0.01 (-0.10, 0.12)	0.08 (-0.06, 0.21)	0.260	0.00004	(-0.00005, 0.00012)	0.393		
model 3		Reference	-0.01 (-0.12, 0.10)	0.00 (-0.11, 0.11)	0.08 (-0.06, 0.21)	0.271	0.00004	(-0.00005, 0.00012)	0.415		
CDT	1652										
crude model		Reference	-0.07 (-0.19, 0.06)	-0.02 (-0.15, 0.10)	-0.07 (-0.23, 0.08)	0.546	-0.00002	(-0.00012, 0.00007)	0.637		
model 1		Reference	-0.08 (-0.19, 0.04)	-0.04 (-0.16, 0.07)	-0.11 (-0.25, 0.04)	0.257	-0.00005	(-0.00013, 0.00004)	0.304		
model 2		Reference	-0.06 (-0.18, 0.05)	-0.04 (-0.15, 0.07)	-0.11 (-0.26, 0.03)	0.195	-0.00005	(-0.00014, 0.00003)	0.219		
model 3		Reference	-0.06 (-0.17, 0.06)	-0.03 (-0.14, 0.09)	-0.10 (-0.25, 0.04)	0.253	-0.00005	(-0.00014, 0.00004)	0.277		
VFT-a	1686										
crude model		Reference	-0.15 (-0.29, -0.01)*	-0.16 (-0.31, -0.02)*	0.08 (-0.10, 0.25)	0.649	0.00001	(-0.00010, 0.00012)	0.821		
model 1		Reference	-0.06 (-0.17, 0.05)	-0.08 (-0.20, 0.03)	0.07 (-0.07, 0.20)	0.592	0.00002	(-0.00007, 0.00010)	0.717		
model 2		Reference	-0.05 (-0.16, 0.06)	-0.08 (-0.19, 0.04)	0.08 (-0.06, 0.21)	0.503	0.00002	(-0.00006, 0.00010)	0.671		
model 3		Reference	-0.05 (-0.16, 0.06)	-0.08 (-0.20, 0.04)	0.08 (-0.06, 0.21)	0.527	0.00002	(-0.00007, 0.00010)	0.718		

PREDIMED-Plus: Water Intake, Hydration, & Cognition

VFT-p	1686										
crude											
model	Reference	-0.07	(-0.21, 0.08)	-0.07	(-0.23, 0.09)	-0.01	(-0.18, 0.16)	0.863	0.00000	(-0.00011, 0.00010)	0.963
model 1	Reference	-0.02	(-0.12, 0.09)	0.00	(-0.11, 0.12)	-0.03	(-0.16, 0.10)	0.838	0.00000	(-0.00008, 0.00008)	0.993
model 2	Reference	0.00	(-0.11, 0.10)	0.01	(-0.10, 0.13)	-0.01	(-0.14, 0.11)	0.971	0.00000	(-0.00008, 0.00008)	0.930
model 3	Reference	-0.01	(-0.12, 0.09)	0.01	(-0.11, 0.12)	-0.01	(-0.14, 0.11)	0.976	0.00000	(-0.00008, 0.00008)	0.923
TMT-A	1683										
crude											
model	Reference	0.04	(-0.09, 0.16)	-0.01	(-0.14, 0.12)	-0.10	(-0.24, 0.05)	0.157	-0.00008	(-0.00017, 0.00002)	0.113
model 1	Reference	-0.01	(-0.11, 0.09)	-0.03	(-0.13, 0.08)	0.00	(-0.11, 0.11)	0.873	-0.00001	(-0.00009, 0.00006)	0.707
model 2	Reference	-0.02	(-0.12, 0.08)	-0.03	(-0.14, 0.07)	-0.01	(-0.12, 0.11)	0.784	-0.00002	(-0.00009, 0.00006)	0.672
model 3	Reference	-0.02	(-0.12, 0.08)	-0.04	(-0.14, 0.07)	-0.01	(-0.12, 0.10)	0.743	-0.00002	(-0.00009, 0.00006)	0.656
TMT-B	1681										
crude											
model	Reference	0.10	(-0.02, 0.23)	0.14	(0.003, 0.27)*	-0.07	(-0.22, 0.08)	0.738	-0.00002	(-0.00012, 0.00007)	0.668
model 1	Reference	0.08	(-0.03, 0.18)	0.06	(-0.05, 0.17)	-0.04	(-0.17, 0.08)	0.555	-0.00002	(-0.00010, 0.00006)	0.568
model 2	Reference	0.07	(-0.03, 0.17)	0.06	(-0.05, 0.17)	-0.04	(-0.16, 0.09)	0.631	-0.00001	(-0.00009, 0.00006)	0.705
model 3	Reference	0.07	(-0.03, 0.17)	0.06	(-0.05, 0.17)	-0.04	(-0.17, 0.09)	0.625	-0.00001	(-0.00009, 0.00006)	0.720
DST-f	1449										
crude											
model	Reference	0.15	(-0.0005, 0.30)	0.13	(-0.02, 0.29)	0.30	(0.11, 0.49)*	0.004	0.00017	(-0.00006, 0.00029)	0.002
model 1	Reference	0.06	(-0.06, 0.17)	0.09	(-0.04, 0.21)	0.15	(-0.002, 0.31)	0.047	0.00010	(-0.00001, 0.00019)	0.031
model 2	Reference	0.08	(-0.04, 0.20)	0.11	(-0.02, 0.24)	0.16	(0.01, 0.31)*	0.029	0.00011	(-0.00002, 0.00020)	0.021
model 3	Reference	0.09	(-0.03, 0.21)	0.11	(-0.01, 0.24)	0.17	(0.02, 0.32)*	0.021	0.00011	(-0.00002, 0.00020)	0.016
DST-b	1449										
crude											
model	Reference	0.15	(0.003, 0.30)*	0.07	(-0.08, 0.23)	0.19	(0.01, 0.38)*	0.132	0.00010	(-0.00001, 0.00021)	0.079
model 1	Reference	0.06	(-0.06, 0.18)	0.02	(-0.11, 0.14)	0.02	(-0.13, 0.17)	0.970	0.00002	(-0.00007, 0.00011)	0.635
model 2	Reference	0.08	(-0.04, 0.20)	0.04	(-0.08, 0.16)	0.05	(-0.10, 0.19)	0.740	0.00003	(-0.00006, 0.00012)	0.481
model 3	Reference	0.08	(-0.04, 0.20)	0.04	(-0.08, 0.16)	0.05	(-0.10, 0.20)	0.691	0.00004	(-0.00005, 0.00012)	0.434

WATER FROM ALL FLUIDS ^d											
Quantiles of Water from All Fluids									Continuous		
	N	Q1 β (95% CI)	Q2 β (95% CI)	Q3 β (95% CI)	Q4 β (95% CI)	p for trend			β (95% CI)	p-value	
GCF	1395	1127 ^e (251 to 1441)	1623 (1445 to 1808)	2005 (1809 to 2222)	2608 (2225 to 3722)						
crude model		Reference	0.02 (-0.13, 0.17)	0.00 (-0.15, 0.15)	0.13 (-0.01, 0.28)	0.085			0.00007 (-0.00002, 0.00015)	0.122	
model 1		Reference	-0.03 (-0.11, 0.06)	-0.04 (-0.13, 0.05)	0.00 (-0.08, 0.08)	0.980			-0.00001 (-0.00006, 0.00004)	0.648	
model 2		Reference	-0.03 (-0.11, 0.06)	-0.05 (-0.14, 0.04)	-0.01 (-0.09, 0.08)	0.851			-0.00002 (-0.00007, 0.00003)	0.499	
model 3		Reference	-0.02 (-0.11, 0.06)	-0.05 (-0.13, 0.04)	0.00 (-0.09, 0.08)	0.870			-0.00002 (-0.00007, 0.00003)	0.506	
MMSE	1651	1121 (251 to 1443)	1621 (1445 to 1808)	2005 (1809 to 2222)	2606 (2225 to 3951)						
crude model		Reference	0.00 (-0.13, 0.13)	-0.02 (-0.15, 0.12)	0.13 (0.003, 0.25)*	0.049			0.00007 (-0.000003, 0.00015)	0.059	
model 1		Reference	-0.06 (-0.18, 0.05)	-0.07 (-0.19, 0.04)	0.03 (-0.08, 0.14)	0.555			0.00001 (-0.00006, 0.00007)	0.844	
model 2		Reference	-0.06 (-0.17, 0.06)	-0.07 (-0.18, 0.04)	0.03 (-0.08, 0.14)	0.599			0.00001 (-0.00006, 0.00007)	0.875	
model 3		Reference	-0.06 (-0.17, 0.06)	-0.07 (-0.18, 0.05)	0.03 (-0.08, 0.14)	0.577			0.00001 (-0.00006, 0.00007)	0.856	
CDT	1652	1119 (251 to 1443)	1620 (1445 to 1808)	2005 (1809 to 2222)	2605 (2225 to 3951)						
crude model		Reference	0.10 (-0.02, 0.23)	0.01 (-0.12, 0.14)	0.11 (-0.02, 0.23)	0.220			0.00007 (-0.000002, 0.00014)	0.055	
model 1		Reference	0.08 (-0.03, 0.19)	-0.02 (-0.15, 0.10)	0.03 (-0.09, 0.14)	0.984			0.00002 (-0.00005, 0.00009)	0.535	
model 2		Reference	0.07 (-0.04, 0.19)	-0.03 (-0.16, 0.09)	0.02 (-0.10, 0.13)	0.840			0.00001 (-0.00005, 0.00008)	0.687	
model 3		Reference	0.08 (-0.04, 0.19)	-0.03 (-0.16, 0.09)	0.00 (-0.12, 0.11)	0.575			0.00000 (-0.00007, 0.00007)	0.984	

PREDIMED-Plus: Water Intake, Hydration, & Cognition

		1118 (251 to 1443)	1620 (1445 to 1808)	2005 (1809 to 2222)	2606 (2225 to 3951)						
VFT-a	1686										
crude		Reference	-0.02 (-0.17, 0.12)	0.01 (-0.13, 0.15)	0.11 (-0.04, 0.25)	0.113	0.00005	(-0.00007, 0.00007)		0.241	
model 1		Reference	-0.06 (-0.17, 0.05)	-0.04 (-0.15, 0.07)	-0.03 (-0.15, 0.08)	0.642	-0.00003	(-0.00009, 0.00004)		0.383	
model 2		Reference	-0.06 (-0.17, 0.05)	-0.04 (-0.15, 0.07)	-0.04 (-0.15, 0.07)	0.558	-0.00003	(-0.00010, 0.00003)		0.323	
model 3		Reference	-0.06 (-0.17, 0.05)	-0.04 (-0.15, 0.07)	-0.04 (-0.15, 0.07)	0.541	-0.00004	(-0.00010, 0.00003)		0.305	
VFT-p	1686										
crude		Reference	0.09 (-0.06, 0.23)	0.06 (-0.08, 0.21)	0.19 (0.05, 0.34)*	0.013	0.00010	(-0.00001, 0.00019)		0.030	
model 1		Reference	0.08 (-0.02, 0.18)	0.01 (-0.09, 0.12)	0.07 (-0.03, 0.18)	0.338	0.00002	(-0.00004, 0.00009)		0.511	
model 2		Reference	0.08 (-0.02, 0.17)	0.01 (-0.10, 0.12)	0.07 (-0.04, 0.17)	0.367	0.00002	(-0.00005, 0.00009)		0.558	
model 3		Reference	0.08 (-0.02, 0.18)	0.02 (-0.09, 0.13)	0.09 (-0.02, 0.20)	0.196	0.00003	(-0.00003, 0.00010)		0.328	
TMT-A	1683										
crude		Reference	-0.11 (-0.24, 0.02)	-0.09 (-0.23, 0.04)	-0.21 (-0.34, -0.07)*	0.003	-0.00010	(-0.00018, 0.00003)		0.009	
model 1		Reference	-0.03 (-0.13, 0.07)	-0.03 (-0.14, 0.08)	-0.02 (-0.12, 0.07)	0.664	0.00000	(-0.00006, 0.00006)		0.929	
model 2		Reference	-0.03 (-0.14, 0.07)	-0.02 (-0.13, 0.08)	-0.02 (-0.12, 0.08)	0.750	0.00001	(-0.00005, 0.00007)		0.821	
model 3		Reference	-0.03 (-0.14, 0.07)	-0.02 (-0.12, 0.09)	-0.02 (-0.12, 0.08)	0.847	0.00001	(-0.00005, 0.00007)		0.724	
TMT-B	1681										
crude		Reference	0.08 (-0.05, 0.21)	0.00 (-0.13, 0.13)	-0.06 (-0.19, 0.06)	0.181	-0.00004	(-0.00012, 0.00004)		0.335	
model 1		Reference	0.07 (-0.03, 0.17)	0.02 (-0.09, 0.13)	0.00 (-0.11, 0.10)	0.731	0.00000	(-0.00006, 0.00007)		0.924	
model 2		Reference	0.08 (-0.02, 0.18)	0.04 (-0.06, 0.15)	0.02 (-0.09, 0.12)	0.976	0.00002	(-0.00005, 0.00008)		0.610	
model 3		Reference	0.08 (-0.02, 0.18)	0.05 (-0.06, 0.15)	0.03 (-0.08, 0.13)	0.802	0.00002	(-0.00004, 0.00009)		0.469	

		1122 (251 to 1442)	1624 (1445 to 1808)	2005 (1809 to 2222)	2609 (2225 to 3722)					
DST-f	1449									
crude		Reference	0.11 (-0.04, 0.25)	0.14 (-0.01, 0.30)	0.27 (0.12, 0.42)*	0.000	0.00017	(-0.00008, 0.00025)	<0.001	
model 1		Reference	0.01 (-0.10, 0.13)	0.04 (-0.09, 0.16)	0.12 (0.01, 0.24)*	0.032	0.00007	(0.00000, 0.00014)	0.048	
model 2		Reference	0.01 (-0.11, 0.12)	0.03 (-0.09, 0.15)	0.12 (0.01, 0.24)*	0.030	0.00007	(0.00000, 0.00014)	0.047	
model 3		Reference	0.00 (-0.11, 0.12)	0.03 (-0.10, 0.15)	0.12 (0.001, 0.24)*	0.041	0.00007	(-0.000005, 0.00014)	0.068	
DST-b	1449									
crude		Reference	0.09 (-0.06, 0.23)	0.10 (-0.05, 0.24)	0.17 (0.03, 0.32)*	0.025	0.00009	(-0.000002, 0.00017)	0.057	
model 1		Reference	-0.02 (-0.13, 0.10)	-0.03 (-0.15, 0.09)	0.04 (-0.08, 0.16)	0.496	0.00001	(-0.00007, 0.00008)	0.855	
model 2		Reference	-0.02 (-0.13, 0.10)	-0.03 (-0.15, 0.09)	0.04 (-0.08, 0.15)	0.505	0.00001	(-0.00006, 0.00008)	0.846	
model 3		Reference	-0.01 (-0.13, 0.10)	-0.03 (-0.15, 0.09)	0.03 (-0.09, 0.15)	0.636	0.00000	(-0.00008, 0.00007)	0.955	
TOTAL WATER^f										
Quantiles of Total Water Intake							Continuous			
	N	Q1 β (95% CI)	Q2 β (95% CI)	Q3 β (95% CI)	Q4 β (95% CI)	p for trend		β (95% CI)		p-value
		2068 (1155 to 2395)	2616 (2400 to 2832)	3059 (2834 to <3308)	3752 (3308 to 5184)					
GCF	1395									
crude		Reference	-0.02 (-0.17, 0.13)	-0.02 (-0.18, 0.13)	0.02 (-0.13, 0.16)	0.792	-0.00001	(-0.00008, 0.00007)	0.817	
model 1		Reference	0.01 (-0.07, 0.09)	-0.06 (-0.15, 0.03)	-0.02 (-0.10, 0.07)	0.439	-0.00002	(-0.00006, 0.00002)	0.382	
model 2		Reference	0.00 (-0.08, 0.09)	-0.06 (-0.15, 0.02)	-0.03 (-0.12, 0.05)	0.264	-0.00003	(-0.00007, 0.00002)	0.201	
model 3		Reference	0.00 (-0.08, 0.09)	-0.07 (-0.16, 0.02)	-0.05 (-0.14, 0.04)	0.137	-0.00004	(-0.00008, 0.00001)	0.088	

PREDIMED-Plus: Water Intake, Hydration, & Cognition

		2063 (1015 to 2395)	2615 (2396 to 2832)	3058 (2832 to <3308)	3741 (3308 to 5184)						
MMSE	1651										
crude		Reference	0.00 (-0.13, 0.13)	0.00 (-0.14, 0.13)	0.08 (-0.05, 0.21)	0.214	0.00003	(-0.00005, 0.00010)		0.496	
model 1		Reference	0.02 (-0.10, 0.13)	-0.07 (-0.19, 0.05)	0.04 (-0.07, 0.16)	0.705	0.00000	(-0.00006, 0.00006)		0.992	
model 2		Reference	0.02 (-0.10, 0.13)	-0.07 (-0.19, 0.05)	0.04 (-0.07, 0.15)	0.705	0.00000	(-0.00006, 0.00006)		0.984	
model 3		Reference	0.02 (-0.10, 0.13)	-0.07 (-0.19, 0.05)	0.04 (-0.07, 0.15)	0.776	-0.00001	(-0.00007, 0.00006)		0.871	
CDT	1652	2061 (1015 to 2395)	2614 (2396 to 2832)	3058 (>2832 to <3308)	3741 (3308 to 5184)						
crude		Reference	-0.01 (-0.13, 0.12)	0.05 (-0.08, 0.17)	0.04 (-0.08, 0.16)	0.380	0.00003	(-0.00004, 0.00009)		0.418	
model 1		Reference	0.00 (-0.12, 0.11)	0.03 (-0.09, 0.14)	0.02 (-0.09, 0.14)	0.590	0.00001	(-0.00005, 0.00007)		0.716	
model 2		Reference	-0.01 (-0.13, 0.11)	0.01 (-0.10, 0.13)	0.01 (-0.11, 0.12)	0.816	0.00000	(-0.00006, 0.00006)		0.976	
model 3		Reference	-0.01 (-0.13, 0.10)	0.00 (-0.12, 0.12)	-0.03 (-0.15, 0.09)	0.712	-0.00002	(-0.00009, 0.00004)		0.520	
VFT-a	1686	2063 (1015 to 2395)	2614 (2396 to 2832)	3059 (>2832 to <3308)	3745 (3308 to 5184)						
crude		Reference	-0.06 (-0.21, 0.08)	0.06 (-0.08, 0.20)	0.03 (-0.12, 0.17)	0.415	0.00003	(-0.00005, 0.00010)		0.497	
model 1		Reference	-0.05 (-0.16, 0.06)	-0.03 (-0.14, 0.08)	-0.06 (-0.17, 0.05)	0.392	-0.00003	(-0.00009, 0.00002)		0.251	
model 2		Reference	-0.05 (-0.16, 0.05)	-0.03 (-0.14, 0.08)	-0.06 (-0.17, 0.05)	0.344	-0.00004	(-0.00010, 0.00002)		0.215	
model 3		Reference	-0.06 (-0.17, 0.05)	-0.04 (-0.15, 0.07)	-0.08 (-0.20, 0.04)	0.236	-0.00005	(-0.00011, 0.00001)		0.125	
VFT-p	1686	2063 (1015 to 2395)	2614 (2396 to 2832)	3059 (>2832 to <3308)	3745 (3308 to 5184)						
crude		Reference	0.06 (-0.08, 0.20)	0.05 (-0.09, 0.20)	0.09 (-0.06, 0.23)	0.275	0.00005	(-0.00003, 0.00013)		0.225	
model 1		Reference	0.05 (-0.03, 0.17)	0.02 (-0.09, 0.13)	-0.01 (-0.12, 0.10)	0.594	0.00000	(-0.00006, 0.00006)		0.907	
model 2		Reference	0.07 (-0.03, 0.17)	0.02 (-0.09, 0.13)	-0.01 (-0.12, 0.09)	0.563	-0.00001	(-0.00007, 0.00005)		0.847	
model 3		Reference	0.07 (-0.03, 0.17)	0.02 (-0.08, 0.13)	0.00 (-0.11, 0.11)	0.745	0.00000	(-0.00006, 0.00007)		0.904	

PREDIMED-Plus: Water Intake, Hydration, & Cognition

		2062 (1015 to 2395)	2614 (2396 to 2832)	3058 (>2832 to <3308)	3744 (3308 to 5184)					
TMT-A	1683									
crude		Reference	-0.06 (-0.19, 0.07)	-0.12 (-0.25, 0.01)	-0.09 (-0.22, 0.05)	0.154	-0.00004	(-0.00011, 0.00003)		0.252
model 1		Reference	-0.05 (-0.15, 0.05)	-0.05 (-0.15, 0.05)	-0.01 (-0.12, 0.10)	0.936	0.00001	(-0.00005, 0.00007)		0.781
model 2		Reference	-0.04 (-0.14, 0.06)	-0.04 (-0.14, 0.06)	0.00 (-0.11, 0.11)	0.880	0.00002	(-0.00004, 0.00007)		0.592
model 3		Reference	-0.04 (-0.14, 0.06)	-0.04 (-0.14, 0.06)	0.02 (-0.10, 0.13)	0.681	0.00003	(-0.00003, 0.00009)		0.382
TMT-B	1681	2063 (1015 to 2395)	2614 (2396 to 2832)	3059 (>2832 to <3308)	3745 (3308 to 5184)					
crude		Reference	0.07 (-0.06, 0.20)	-0.03 (-0.16, 0.10)	-0.01 (-0.14, 0.12)	0.600	-0.00001	(-0.00008, 0.00006)		0.686
model 1		Reference	0.07 (-0.04, 0.17)	-0.01 (-0.12, 0.10)	0.01 (-0.10, 0.11)	0.786	0.00000	(-0.00006, 0.00006)		0.984
model 2		Reference	0.08 (-0.03, 0.18)	0.01 (-0.10, 0.11)	0.03 (-0.07, 0.13)	0.840	0.00001	(-0.00004, 0.00007)		0.667
model 3		Reference	0.08 (-0.02, 0.18)	0.02 (-0.08, 0.12)	0.06 (-0.05, 0.16)	0.498	0.00003	(-0.00003, 0.00009)		0.320
DST-f	1449	2068 (1155 to 2395)	2615 (2401 to 2832)	3060 (2834 to <3308)	3754 (3308 to 5184)					
crude		Reference	0.13 (-0.03, 0.28)	0.06 (-0.10, 0.21)	0.15 (-0.01, 0.30)	0.128	0.00008	(-0.000002, 0.00016)		0.057
model 1		Reference	0.06 (-0.06, 0.18)	-0.01 (-0.13, 0.11)	0.06 (-0.07, 0.18)	0.584	0.00005	(-0.00002, 0.00011)		0.160
model 2		Reference	0.06 (-0.05, 0.18)	-0.01 (-0.13, 0.11)	0.05 (-0.07, 0.18)	0.618	0.00004	(-0.00002, 0.00011)		0.175
model 3		Reference	0.06 (-0.06, 0.18)	0.00 (-0.13, 0.12)	0.06 (-0.07, 0.19)	0.547	0.00005	(-0.00002, 0.00012)		0.144
DST-b	1449	2068 (1155 to 2395)	2615 (2401 to 2832)	3060 (2834 to <3308)	3754 (3308 to 5184)					
crude		Reference	0.00 (-0.15, 0.15)	0.03 (-0.12, 0.18)	0.02 (-0.13, 0.16)	0.780	0.00000	(-0.00008, 0.00008)		0.985
model 1		Reference	-0.04 (-0.16, 0.08)	-0.07 (-0.19, 0.04)	-0.04 (-0.15, 0.08)	0.513	-0.00001	(-0.00007, 0.00006)		0.860
model 2		Reference	-0.03 (-0.15, 0.09)	-0.07 (-0.18, 0.05)	-0.03 (-0.15, 0.08)	0.495	-0.00001	(-0.00007, 0.00005)		0.789
model 3		Reference	-0.03 (-0.15, 0.09)	-0.08 (-0.19, 0.03)	-0.06 (-0.18, 0.06)	0.272	-0.00002	(-0.00009, 0.00004)		0.463

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across categories of hydration status and various modes of water/fluid intake, as well as continuous associations between cognitive function variables and hydration status/fluid intake.

Multivariable model 1: adjusted for baseline corresponding cognitive function score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center (≤ 100 , 100 to < 200 , 200 to < 300 , > 300 participants).

Multivariable model 2: additionally adjusted for body mass index (kg/m²), educational level (primary, secondary or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), and physical activity (METs/min/day).

Multivariable model 3: additionally adjusted for 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).

^aWater Intake represents fluid water consumed as a beverage, including tap and bottled forms of water.

^bContinuous analysis based on 100 ml increments of water intake from the noted sources.

^cGCF represents global cognitive function, and was calculated using a composite of z-scores using the formula: $GCF = (zMMSE + zCDT + zVFT-a + zVFT-b + (-zTMT-A) + (-zTMT-B) + zDST-f + zDST-b) / 8$.

Where MMSE, CDT, VFT-a, VFT-p, TMT-A, TMT-B, DST-f, and DST-b are various cognitive function tests that were included in the battery of neuropsychological tests.

^dWater from all fluids represents water consumed from all beverages.

^eThe first row of each cognitive performance assessment from this point on provides the mean and range (ml/day) of the respective fluid exposure for each quantile indicated.

^fTotal Water represents water consumed via beverage and food sources.

*Indicates within group significance ($p < 0.05$).

Abbreviations: CDT, Clock Drawing Test; DST-b, Digit Span test-backward; DST-f, Digit Span test -forward; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; Q, quantile; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

Supplemental Table 3. Multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in cognitive performance according to EFSA fluid intake related guidelines in the PREDIMED-Plus cohort.

EFSA GUIDANCE^a FOR TOTAL FLUID WATER INTAKE (EFSA TFWI)					
Total Fluid Water Intake Mean, Range (ml/day)		Does Not Meet Recommendations 1384 (251 to 1997) β (95% CI)	Meets Recommendations 2271 (1601 to 4398) β (95% CI)		p for trend
	N				
GCF^b	1395				
crude model		Reference	-0.11	(-0.22, -0.01)	0.037
model 1		Reference	-0.02	(-0.08, 0.04)	0.481
model 2		Reference	-0.02	(-0.08, 0.04)	0.446
model 3		Reference	-0.03	(-0.09, 0.03)	0.375
MMSE	1651				
crude model		Reference	-0.01	(-0.10, 0.08)	0.781
model 1		Reference	0.03	(-0.05, 0.11)	0.439
model 2		Reference	0.03	(-0.05, 0.12)	0.407
model 3		Reference	0.03	(-0.05, 0.11)	0.467
CDT	1652				
crude model		Reference	0.02	(-0.06, 0.11)	0.578
model 1		Reference	0.05	(-0.03, 0.13)	0.233
model 2		Reference	0.05	(-0.04, 0.13)	0.277
model 3		Reference	0.03	(-0.05, 0.11)	0.489
VFT-a	1686				
crude model		Reference	-0.06	(-0.17, 0.04)	0.206
model 1		Reference	-0.02	(-0.09, 0.06)	0.684
model 2		Reference	-0.01	(-0.09, 0.06)	0.729
model 3		Reference	-0.02	(-0.10, 0.06)	0.608
VFT-p	1686				
crude model		Reference	0.02	(-0.09, 0.12)	0.770
model 1		Reference	0.00	(-0.08, 0.08)	0.998
model 2		Reference	0.01	(-0.07, 0.08)	0.865
model 3		Reference	0.02	(-0.06, 0.09)	0.667
TMT-A	1683				
crude model		Reference	-0.02	(-0.10, 0.07)	0.721
model 1		Reference	0.01	(-0.06, 0.08)	0.784
model 2		Reference	0.01	(-0.06, 0.08)	0.824
model 3		Reference	0.01	(-0.06, 0.09)	0.696
TMT-B	1681				
crude model		Reference	0.09	(-0.003, 0.18)	0.059
model 1		Reference	0.00	(-0.08, 0.07)	0.900
model 2		Reference	0.00	(-0.07, 0.07)	0.960
model 3		Reference	0.01	(-0.06, 0.09)	0.714

DST-f	1449				
crude model		Reference	-0.02	(-0.13, 0.09)	0.693
model 1		Reference	0.02	(-0.07, 0.11)	0.693
model 2		Reference	0.02	(-0.06, 0.11)	0.582
model 3		Reference	0.02	(-0.07, 0.11)	0.663
DST-b	1449				
crude model		Reference	-0.06	(-0.17, 0.04)	0.241
model 1		Reference	-0.03	(-0.12, 0.05)	0.431
model 2		Reference	-0.03	(-0.11, 0.06)	0.548
model 3		Reference	-0.03	(-0.12, 0.05)	0.430

EFSA GUIDANCE^a FOR TOTAL WATER INTAKE (EFSA TWI)

Total Water Intake Mean, Range (ml/day)		Does Not Meet Recommendations 2054 (1015 to 2499)	Meets Recommendations 3073 (2002 to 5794)		
	N	β (95% CI)	β	(95% CI)	p for trend
GCF^b	1395				
crude model		Reference	-0.25	(-0.38, -0.12)	<0.001
model 1		Reference	-0.05	(-0.13, 0.03)	0.233
model 2		Reference	-0.05	(-0.13, 0.02)	0.165
model 3		Reference	-0.06	(-0.14, 0.02)	0.116
MMSE	1651				
crude model		Reference	-0.07	(-0.19, 0.04)	0.229
model 1		Reference	0.00	(-0.10, 0.10)	0.989
model 2		Reference	0.00	(-0.10, 0.11)	0.935
model 3		Reference	0.00	(-0.10, 0.11)	0.935
CDT	1652				
crude model		Reference	-0.11	(-0.22, -0.01)	0.036
model 1		Reference	-0.03	(-0.13, 0.07)	0.555
model 2		Reference	-0.04	(-0.14, 0.06)	0.393
model 3		Reference	-0.06	(-0.17, 0.04)	0.224
VFT-a	1686				
crude model		Reference	-0.15	(-0.27, -0.02)	0.025
model 1		Reference	-0.03	(-0.13, 0.07)	0.561
model 2		Reference	-0.03	(-0.13, 0.07)	0.539
model 3		Reference	-0.04	(-0.14, 0.07)	0.468
VFT-p	1686				
crude model		Reference	-0.06	(-0.19, 0.07)	0.386
model 1		Reference	-0.02	(-0.12, 0.08)	0.704
model 2		Reference	-0.02	(-0.12, 0.08)	0.692
model 3		Reference	-0.01	(-0.11, 0.09)	0.787
TMT-A	1683				
crude model		Reference	0.04	(-0.08, 0.16)	0.526
model 1		Reference	-0.05	(-0.15, 0.05)	0.296
model 2		Reference	-0.05	(-0.14, 0.05)	0.344
model 3		Reference	-0.04	(-0.14, 0.05)	0.394

TMT-B	1681				
crude model		Reference	0.15	(0.04, 0.26)	0.007
model 1		Reference	-0.01	(-0.10, 0.09)	0.877
model 2		Reference	0.01	(-0.09, 0.10)	0.891
model 3		Reference	0.02	(-0.07, 0.11)	0.684
DST-f	1449				
crude model		Reference	-0.13	(-0.28, 0.01)	0.069
model 1		Reference	-0.02	(-0.13, 0.10)	0.783
model 2		Reference	-0.02	(-0.13, 0.09)	0.762
model 3		Reference	-0.01	(-0.13, 0.10)	0.833
DST-b	1449				
crude model		Reference	-0.18	(-0.32, -0.04)	0.014
model 1		Reference	-0.04	(-0.15, 0.07)	0.473
model 2		Reference	-0.04	(-0.15, 0.07)	0.504
model 3		Reference	-0.05	(-0.16, 0.06)	0.362

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across categories of hydration status and various modes of water/fluid intake, as well as continuous associations between cognitive function variables and hydration status/fluid intake.

Multivariable model 1: adjusted for baseline corresponding cognitive function score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center (≤ 100 , 100 to < 200 , 200 to < 300 , > 300 participants).

Multivariable model 2: additionally adjusted for body mass index (kg/m²), educational level (primary, secondary or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), and physical activity (METs/min/day).

Multivariable model 3: additionally adjusted for 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).

^aBased on the regulations and guidance of the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA): Scientific Opinion on Dietary reference values for water. Where 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, and 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.

^bGCF represents global cognitive function, and was calculated using a composite of z-scores using the formula: $GCF = (zMMSE + zCDT + zVFT-a + zVFT-b + (-zTMT-A) + (-zTMT-B) + zDST-f + zDST-b) / 8$.

Where MMSE, CDT, VFT-a, VFT-p, TMT-A, TMT-B, DST-f, and DST-b are various cognitive function tests that were included in the battery of neuropsychological tests.

Abbreviations: CDT, Clock Drawing Test; DST-b, Digit Span test-backward; DST-f, Digit Span test - forward; EFSA, European Food Safety Authority; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; Q, quantile; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

Supplemental Table 4. Multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in cognitive performance according to hydration status in the PREDIMED-Plus cohort.

HYDRATION STATUS (SOSM ^a)									
		Categorical					Continuous		
SOSM (mmol/L, range)		263 to 294	295 to 299		≥300				
	N	β (95% CI)	β	(95% CI)	β	(95% CI)	p for trend	β	(95% CI) p-value
GCF ^b	877								
crude model		Reference	0.11	(-0.14, 0.37)	-0.08	(-0.32, 0.17)	0.073	-0.013	(-0.026, -0.001) 0.041
model 1		Reference	-0.05	(-0.18, 0.09)	-0.09	(-0.22, 0.05)	0.147	-0.009	(-0.016, -0.002) 0.008
model 2		Reference	-0.06	(-0.19, 0.08)	-0.09	(-0.22, 0.03)	0.110	-0.009	(-0.016, -0.003) 0.006
model 3		Reference	-0.06	(-0.19, 0.08)	-0.11	(-0.24, 0.02)	0.058	-0.010	(-0.017, -0.004) 0.002
MMSE	996								
crude model		Reference	0.12	(-0.10, 0.33)	0.08	(-0.13, 0.29)	0.774	0.005	(-0.006, 0.015) 0.355
model 1		Reference	0.11	(-0.08, 0.30)	0.08	(-0.11, 0.26)	0.747	0.005	(-0.004, 0.014) 0.301
model 2		Reference	0.11	(-0.08, 0.29)	0.08	(-0.10, 0.26)	0.738	0.005	(-0.004, 0.014) 0.289
model 3		Reference	0.10	(-0.08, 0.29)	0.07	(-0.12, 0.26)	0.814	0.005	(-0.005, 0.015) 0.298
CDT	997								
crude model		Reference	0.08	(-0.14, 0.30)	0.04	(-0.17, 0.25)	0.956	-0.006	(-0.016, 0.004) 0.236
model 1		Reference	0.06	(-0.13, 0.25)	0.03	(-0.16, 0.22)	0.989	-0.007	(-0.017, 0.003) 0.159
model 2		Reference	0.05	(-0.15, 0.24)	0.02	(-0.17, 0.21)	0.997	-0.007	(-0.017, 0.003) 0.193
model 3		Reference	0.04	(-0.16, 0.24)	0.02	(-0.18, 0.21)	0.944	-0.007	(-0.017, 0.004) 0.200
VFT-a	1004								
crude model		Reference	-0.11	(-0.35, 0.13)	-0.14	(-0.37, 0.08)	0.230	-0.004	(-0.017, 0.009) 0.557
model 1		Reference	-0.11	(-0.30, 0.09)	-0.15	(-0.34, 0.05)	0.148	-0.009	(-0.019, 0.001) 0.067
model 2		Reference	-0.12	(-0.31, 0.07)	-0.15	(-0.34, 0.03)	0.143	-0.009	(-0.019, 0.000) 0.061
model 3		Reference	-0.12	(-0.31, 0.07)	-0.15	(-0.34, 0.05)	0.172	-0.009	(-0.019, 0.001) 0.091

VFT-p	1004									
crude model		Reference	-0.03	(-0.25, 0.19)	-0.19	(-0.40, 0.03)	0.016	-0.010	(-0.023, 0.002)	0.091
model 1		Reference	-0.06	(-0.24, 0.11)	-0.06	(-0.23, 0.11)	0.668	0.001	(-0.008, 0.010)	0.758
model 2		Reference	-0.07	(-0.24, 0.10)	-0.06	(-0.23, 0.10)	0.609	0.000	(-0.008, 0.009)	0.929
model 3		Reference	-0.08	(-0.25, 0.10)	-0.08	(-0.25, 0.09)	0.491	0.000	(-0.010, 0.009)	0.921
TMT-A	1002									
crude model		Reference	-0.12	(-0.37, 0.13)	0.00	(-0.25, 0.24)	0.359	0.004	(-0.007, 0.016)	0.466
model 1		Reference	-0.09	(-0.27, 0.10)	-0.06	(-0.25, 0.13)	0.806	0.000	(-0.010, 0.010)	0.991
model 2		Reference	-0.07	(-0.26, 0.11)	-0.05	(-0.24, 0.14)	0.890	0.001	(-0.009, 0.010)	0.909
model 3		Reference	-0.08	(-0.27, 0.11)	-0.06	(-0.25, 0.13)	0.784	0.000	(-0.010, 0.009)	0.937
TMT-B	999									
crude model		Reference	-0.15	(-0.40, 0.11)	-0.06	(-0.31, 0.19)	0.822	0.007	(-0.006, 0.019)	0.315
model 1		Reference	-0.08	(-0.30, 0.14)	-0.12	(-0.33, 0.10)	0.234	0.001	(-0.011, 0.013)	0.921
model 2		Reference	-0.08	(-0.29, 0.13)	-0.12	(-0.33, 0.09)	0.209	0.000	(-0.011, 0.012)	0.963
model 3		Reference	-0.09	(-0.30, 0.12)	-0.13	(-0.34, 0.07)	0.172	0.000	(-0.012, 0.012)	0.987
DST-f	901									
crude model		Reference	0.05	(-0.25, 0.35)	0.03	(-0.26, 0.32)	0.974	0.001	(-0.013, 0.014)	0.939
model 1		Reference	-0.05	(-0.25, 0.14)	-0.07	(-0.26, 0.12)	0.488	-0.004	(-0.014, 0.006)	0.435
model 2		Reference	-0.08	(-0.28, 0.11)	-0.10	(-0.29, 0.09)	0.365	-0.005	(-0.015, 0.005)	0.292
model 3		Reference	-0.07	(-0.27, 0.12)	-0.09	(-0.28, 0.10)	0.418	-0.006	(-0.016, 0.004)	0.263
DST-b	901									
crude model		Reference	0.17	(-0.11, 0.45)	0.10	(-0.17, 0.36)	0.951	0.000	(-0.012, 0.013)	0.946
model 1		Reference	0.07	(-0.16, 0.30)	0.02	(-0.19, 0.24)	0.835	-0.001	(-0.011, 0.010)	0.898
model 2		Reference	0.04	(-0.17, 0.26)	0.00	(-0.20, 0.21)	0.740	-0.002	(-0.013, 0.008)	0.674
model 3		Reference	0.05	(-0.17, 0.26)	-0.02	(-0.22, 0.19)	0.518	-0.005	(-0.015, 0.006)	0.402

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across categories of hydration status, as well as continuous associations between cognitive function variables and hydration status.

Multivariable model 1: adjusted for baseline corresponding cognitive function score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center (≤ 100 , 100 to <150 , 150 to <200 , >200 participants).

Multivariable model 2: additionally adjusted for body mass index (kg/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).

Multivariable model 3: additionally adjusted for 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).

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

SOSM >300 mmol/L represented dehydration, 295 to 300 mmol/L represented impending dehydration, and <294 mmol/L represented hydration.

^bGCF represents global cognitive function, and was calculated using a composite of z-scores in the formula: $\text{GCF} = (\text{zMMSE} + \text{zCDT} + \text{zVFT-a} + \text{zVFT-b} + (-\text{zTMT-A}) + (-\text{zTMT-B}) + \text{zDST-f} + \text{zDST-b}) / 8$.

Where MMSE, CDT, VFT-a, VFT-p, TMT-A, TMT-B, DST-f, and DST-b are various cognitive function tests that were included in the battery of neuropsychological tests.

Abbreviations: CDT, Clock Drawing Test; DST-b, Digit Span test-backward; DST-f, Digit Span test -forward; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

Supplemental Table 5. Sensitivity analysis of the multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in global cognitive function (GCF^a, n=1395) according to water and fluid intake related exposures in the PREDIMED-Plus cohort.

WATER INTAKE (BEVERAGE) ^b										
Intake Range (ml/day)	Categorical						Continuous ^c			
	<500	500 to 1000		1000 to 1500		>1500	p for trend	β (95% CI)		p-value
	β (95% CI)	β	(95% CI)	β	(95% CI)	β (95% CI)				
Model 3 + eGFR ^d	Reference	0.01	(-0.07, 0.09)	0.00	(-0.09, 0.08)	-0.01 (-0.11, 0.09)	0.761	-0.00001	(-0.00007, 0.00005)	0.805
Model 3 + Dietary Factors ^e	Reference	-0.07	(-0.21, 0.08)	-0.07	(-0.23, 0.09)	-0.01 (-0.18, 0.16)	0.863	0.00000	(-0.00011, 0.00010)	0.963
Model 3 + MMSE<24 ^f	Reference	0.08	(-0.03, 0.18)	0.06	(-0.05, 0.17)	-0.04 (-0.17, 0.08)	0.555	-0.00002	(-0.00010, 0.00006)	0.568
Model 3 + GCF [<5 and >95%] ^g	Reference	0.08	(-0.03, 0.18)	0.06	(-0.05, 0.17)	-0.04 (-0.17, 0.08)	0.555	-0.00002	(-0.00010, 0.00006)	0.568
WATER FROM ALL FLUIDS ^h										
	Quantiles of Water from All Fluids						Continuous ^c			
	Q1	Q2		Q3		Q4	p for trend	β (95% CI)		p-value
	β (95% CI)	β	(95% CI)	β	(95% CI)	β (95% CI)				
Model 3 + eGFR ^d	Reference	-0.03	(-0.11, 0.06)	-0.04	(-0.13, 0.05)	0.00 (-0.08, 0.08)	0.980	-0.00001	(-0.00006, 0.00004)	0.648
Model 3 + Dietary Factors ^e	Reference	-0.06	(-0.17, 0.05)	-0.04	(-0.15, 0.07)	-0.03 (-0.15, 0.08)	0.642	-0.00003	(-0.00009, 0.00004)	0.383
Model 3 + MMSE<24 ^f	Reference	0.07	(-0.03, 0.17)	0.02	(-0.09, 0.13)	0.00 (-0.11, 0.10)	0.731	0.00000	(-0.00006, 0.00007)	0.924
Model 3 + GCF [<5 and >95%] ^g	Reference	-0.01	(-0.13, 0.10)	-0.03	(-0.15, 0.09)	0.03 (-0.09, 0.15)	0.636	0.00000	(-0.00008, 0.00007)	0.955
TOTAL WATER ⁱ										
	Quantiles of Total Water Intake						Continuous ^c			
	Q1	Q2		Q3		Q4	p for trend	β (95% CI)		p-value
	β (95% CI)	β	(95% CI)	β	(95% CI)	β (95% CI)				
Model 3 + eGFR ^d	Reference	0.01	(-0.07, 0.09)	-0.06	(-0.15, 0.03)	-0.02 (-0.10, 0.07)	0.439	-0.00002	(-0.00006, 0.00002)	0.382
Model 3 + Dietary Factors ^e	Reference	-0.05	(-0.16, 0.06)	-0.03	(-0.14, 0.08)	-0.06 (-0.17, 0.05)	0.392	-0.00003	(-0.00009, 0.00002)	0.251
Model 3 + MMSE<24 ^f	Reference	0.07	(-0.06, 0.20)	-0.03	(-0.16, 0.10)	-0.01 (-0.14, 0.12)	0.600	-0.00001	(-0.00008, 0.00006)	0.686
Model 3 + GCF [<5 and >95%] ^g	Reference	0.07	(-0.06, 0.20)	-0.03	(-0.16, 0.10)	-0.01 (-0.14, 0.12)	0.600	-0.00001	(-0.00008, 0.00006)	0.686

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across categories of hydration status and various modes of water/fluid intake, as well as continuous associations between cognitive function variables and hydration status/fluid intake.

Multivariable model 3: adjusted for baseline corresponding cognitive function score, age (years), sex, intervention PREDIMED-Plus randomized group, participating center (≤ 100 , 100 to < 200 , 200 to < 300 , > 300 participants), body mass index (kg/m^2), educational level (primary, secondary or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), and physical activity ($\text{METs}/\text{min}/\text{day}$), 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).

^aGCF represents global cognitive function, and was calculated using a composite of z-scores using the formula: $\text{GCF} = (\text{zMMSE} + \text{zCDT} + \text{zVFT-a} + \text{zVFT-b} + (-\text{zTMT-A}) + (-\text{zTMT-B}) + \text{zDST-f} + \text{zDST-b}) / 8$.

Where MMSE, CDT, VFT-a, VFT-p, TMT-A, TMT-B, DST-f, and DST-b are various cognitive function tests that were included in the battery of neuropsychological tests.

^bWater Intake represents fluid water consumed as a beverage, including tap and bottled forms of water.

^cContinuous analysis based on 100 ml increments of water intake from the noted sources.

^deGFR represents estimated glomerular filtration rate, an indicator of renal function derived based on serum creatinine level, age and sex.

^eDietary factors represent dietary intake covariates (amount [g/day] of vegetables, fruit, legumes, grains, non-fluid dairy, meat, oils, fish, nuts, and pastries determined via the validated 143-item semi-quantitative Food Frequency Questionnaire (FFQ).

^fMMSE < 24 refers to the removal of participants with baseline MMSE values < 24 .

^gGCF [$< 5\%$ and $> 95\%$] refers to the removal of participants with extreme GCF z-scores at baseline, specifically $< 5\%$ and $> 95\%$.

^hWater from all fluids represents water consumed from all beverages.

ⁱTotal Water represents water consumed via beverage and food sources.

Abbreviations: CDT, Clock Drawing Test; DST-b, Digit Span test-backward; DST-f, Digit Span test -forward; eGFR, estimated Glomerular Filtration Rate; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; Model 3, Multivariable Model 3 (defined above); Q, quantile; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

Supplemental Table 6. Sensitivity analysis of the multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in global cognitive function (GCF^a, n=1395) according to EFSA fluid intake related guidelines in the PREDIMED-Plus cohort.

EFSA GUIDANCE^b FOR TOTAL FLUID WATER INTAKE (EFSA TFWI)				
Total Fluid Water Intake	Does Not Meet Recommendations β (95% CI)	Meets Recommendations β (95% CI)	p for trend	
Model 3 + eGFR ^d	Reference	-0.03 (-0.09, 0.03)	0.313	
Model 3 + Dietary Factors ^d	Reference	-0.01 (-0.09, 0.03)	0.643	
Model 3 + MMSE<24 ^e	Reference	-0.02 (-0.08, 0.04)	0.449	
Model 3 + GCF [<5 and $>95\%$] ^f	Reference	-0.02 (-0.08, 0.04)	0.577	

EFSA GUIDANCE^b FOR TOTAL WATER INTAKE (EFSA TWI)				
Total Water Intake	Does Not Meet Recommendations β (95% CI)	Meets Recommendations β (95% CI)	p for trend	
Model 3 + eGFR ^d	Reference	-0.08 (-0.15, 0.00)	0.047	
Model 3 + Dietary Factors ^d	Reference	-0.06 (-0.14, 0.02)	0.116	
Model 3 + MMSE<24 ^e	Reference	-0.06 (-0.14, 0.01)	0.111	
Model 3 + GCF [<5 and $>95\%$] ^f	Reference	-0.07 (-0.15, 0.01)	0.068	

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across categories of hydration status and various modes of water/fluid intake, as well as continuous associations between cognitive function variables and hydration status/fluid intake.

Multivariable model 3: adjusted for baseline corresponding cognitive function score, age (years), sex, intervention PREDIMED-Plus randomized group, participating center (≤ 100 , 100 to <200 , 200 to <300 , >300 participants), for body mass index (kg/m²), 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).

^aGCF represents global cognitive function, and was calculated using a composite of z-scores using the formula: $GCF = (zMMSE + zCDT + zVFT-a + zVFT-b + (-zTMT-A) + (-zTMT-B) + zDST-f + zDST-b) / 8$.

Where MMSE, CDT, VFT-a, VFT-p, TMT-A, TMT-B, DST-f, and DST-b are various cognitive function tests that were included in the battery of neuropsychological tests.

^bBased on the regulations and guidance of the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA): Scientific Opinion on Dietary reference values for water. Where 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, and 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: CDT, Clock Drawing Test; DST-b, Digit Span test-backward; DST-f, Digit Span test -forward; EFSA, European Food Safety Authority; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; Multivariable Model 3 (defined above); Q, quantile; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

Supplemental Table 7. Sensitivity analysis of the multivariable adjusted mean 2-year change (β -coefficients and 95% CIs) in global cognitive function (GCF^a) according to hydration status in the PREDIMED-Plus cohort.

HYDRATION STATUS (SOSM ^b)									
SOSM (mmol/L, range)	Categorical						Continuous		
	N	263 to 294 β (95% CI)	295 to 299 β (95% CI)	≥ 300 β (95% CI)		p for trend	β (95% CI)		p-value
Model 3 + eGFR ^c	873	Reference	-0.05 (-0.18, 0.08)	-0.10 (-0.23, 0.03)		0.079	-0.010 (-0.017, -0.003)		0.003
Model 3 + Dietary Factors ^d	875	Reference	-0.07 (-0.21, 0.06)	-0.12 (-0.26, 0.01)		0.048	-0.011 (-0.018, -0.004)		0.001
Model 3 + MMSE<24 ^e	849	Reference	-0.07 (-0.20, 0.06)	-0.12 (-0.25, 0.01)		0.046	-0.010 (-0.017, 0.004)		0.002
Model 3 + GCF [<5 and $>95\%$] ^f	710	Reference	-0.03 (-0.17, 0.12)	-0.07 (-0.21, 0.08)		0.235	-0.009 (-0.017, 0.001)		0.025

Multivariable linear regression was used to assess longitudinal association to compare the 2-year changes in cognitive function across categories of hydration status, as well as continuous associations between cognitive function variables and hydration status.

Multivariable model 3: adjusted for baseline corresponding cognitive function score, age (years), sex, intervention PREDIMED-Plus randomized group, participating center (≤ 100 , 100 to <150 , 150 to <200 , >200 participants), body mass index (kg/m^2), educational level (primary, secondary or college), civil status (single, divorced or separated; married; widower), smoking status (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).

^aGCF represents global cognitive function, and was calculated using a composite of z-scores using the formula: $\text{GCF} = (\text{zMMSE} + \text{zCDT} + \text{zVFT-a} + \text{zVFT-b} + (-\text{zTMT-A}) + (-\text{zTMT-B}) + \text{zDST-f} + \text{zDST-b}) / 8$.

Where MMSE, CDT, VFT-a, VFT-p, TMT-A, TMT-B, DST-f, and DST-b are various cognitive function tests that were included in the battery of neuropsychological tests.

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

^ceGFR represents estimated glomerular filtration rate, an indicator of renal function derived based on serum creatinine level, age, and sex.

^dDietary factors represent dietary intake covariates (amount [g/day] of vegetables, fruit, legumes, grains, non-fluid dairy, meat, oils, fish, nuts, and pastries determined via the validated 143-item semi-quantitative Food Frequency Questionnaire (FFQ).

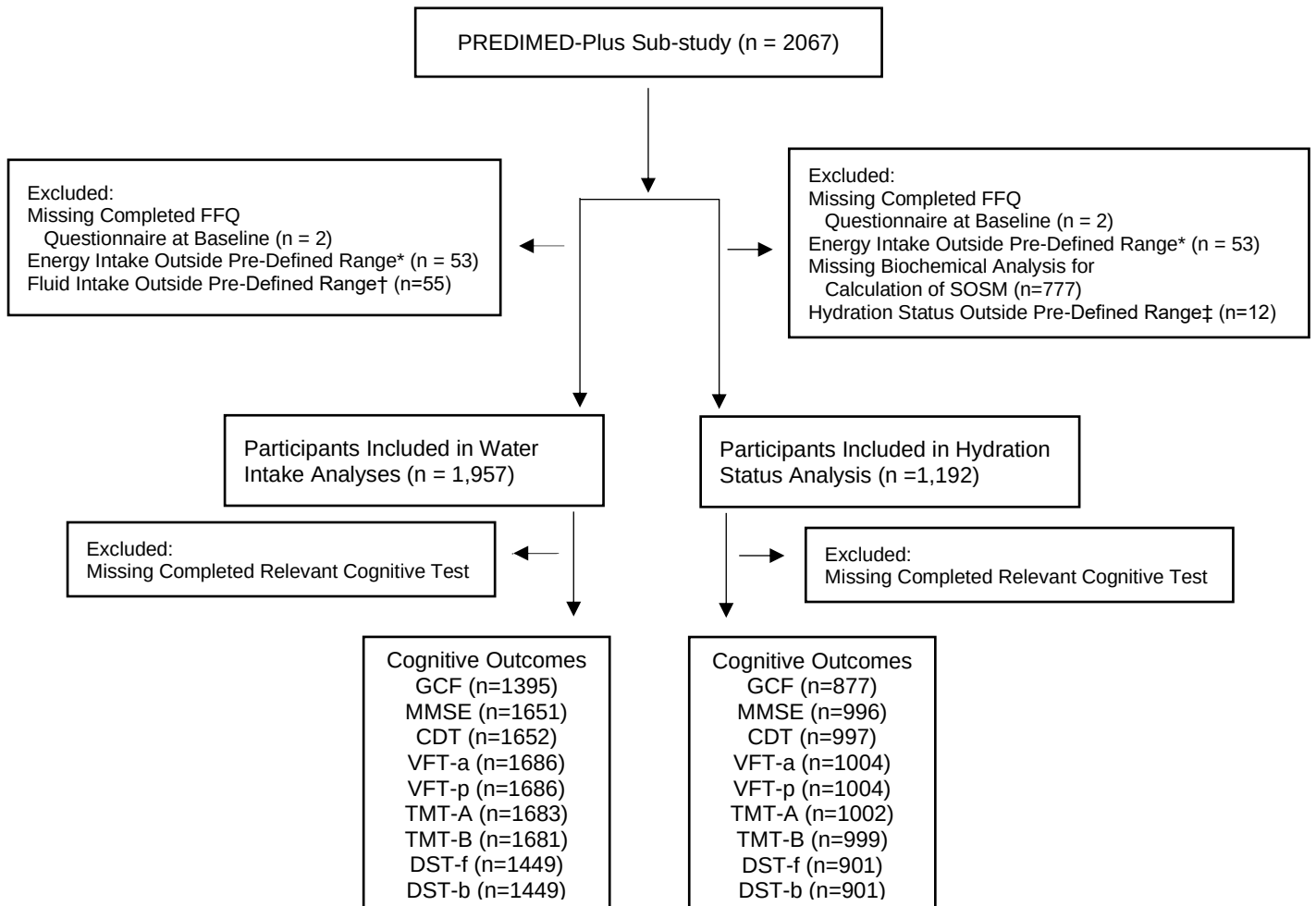
^eMMSE <24 refers to the removal of participants with baseline MMSE values <24 .

^fGCF [<5% and >95%] refers to the removal of participants with extreme GCF z-scores at baseline, specifically <5% and >95%.

Abbreviations: CDT, Clock Drawing Test; DST-b, Digit Span test-backward; DST-f, Digit Span test -forward; eGFR, estimated Glomerular Filtration Rate; GCF, Global Cognitive Function; MMSE, Mini-Mental State Examination; Model 3, Multivariable Model 3 (defined above); Q, quantile; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT-a, Verbal Fluency tasks semantical; VFT-p, Verbal Fluency tasks phonological.

FIGURES

Figure 1. Flow diagram of participants in the PREDIMED-Plus sub-study for the analysis of a priori water intake and hydration status and cognitive performance in the PREDIMED-Plus trial.



* Energy intakes outside pre-specified limits were defined as ≤ 800 kcal/d or ≥ 4000 kcal/d for men and ≤ 500 kcal/d or ≥ 3500 kcal/d for women.

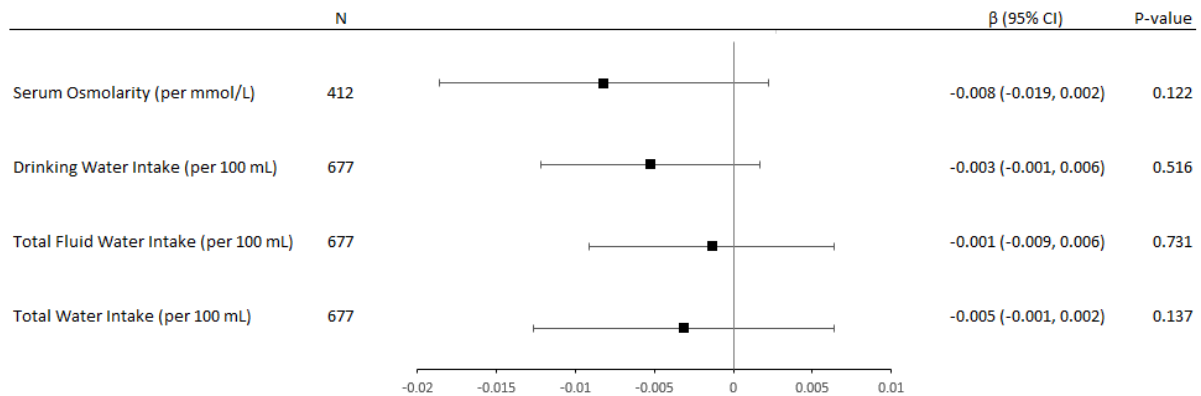
+Fluid intakes outside pre-specified limits were defined as < 490 ml/day or > 3262 ml/day for men and < 397 ml/day or > 3590 ml/day for women or considered “outliers” (using the interquartile range method, by sex).

‡Hydration status outside pre-specified limits were defined as calculated serum osmolality below < 100 mmol/L.

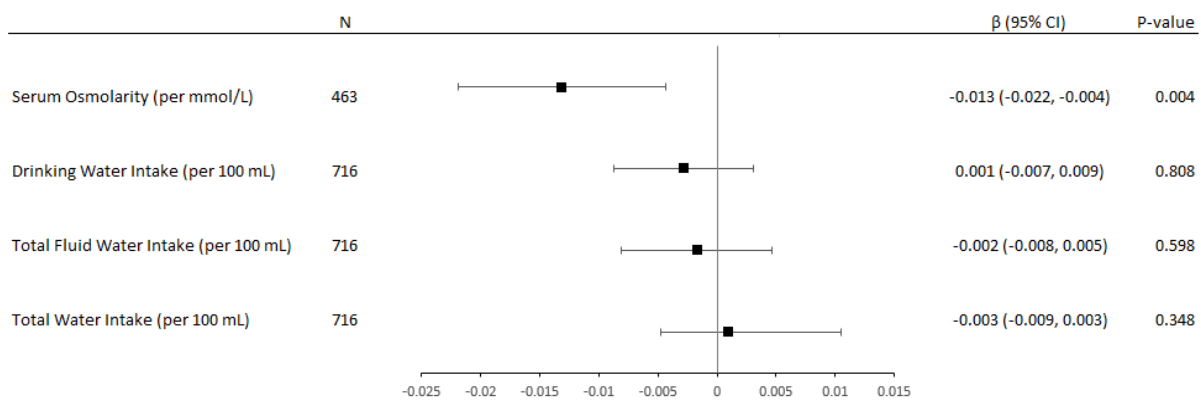
Abbreviations: FFQ, food frequency questionnaire; SOSM, serum osmolality.

Figure 2. Beta-coefficients and 95% CI for hydration status and water and fluid intakes continuously with 2-year changes in global cognitive function (z-scores) in women (A) and men (B).

A) Women



B) Men

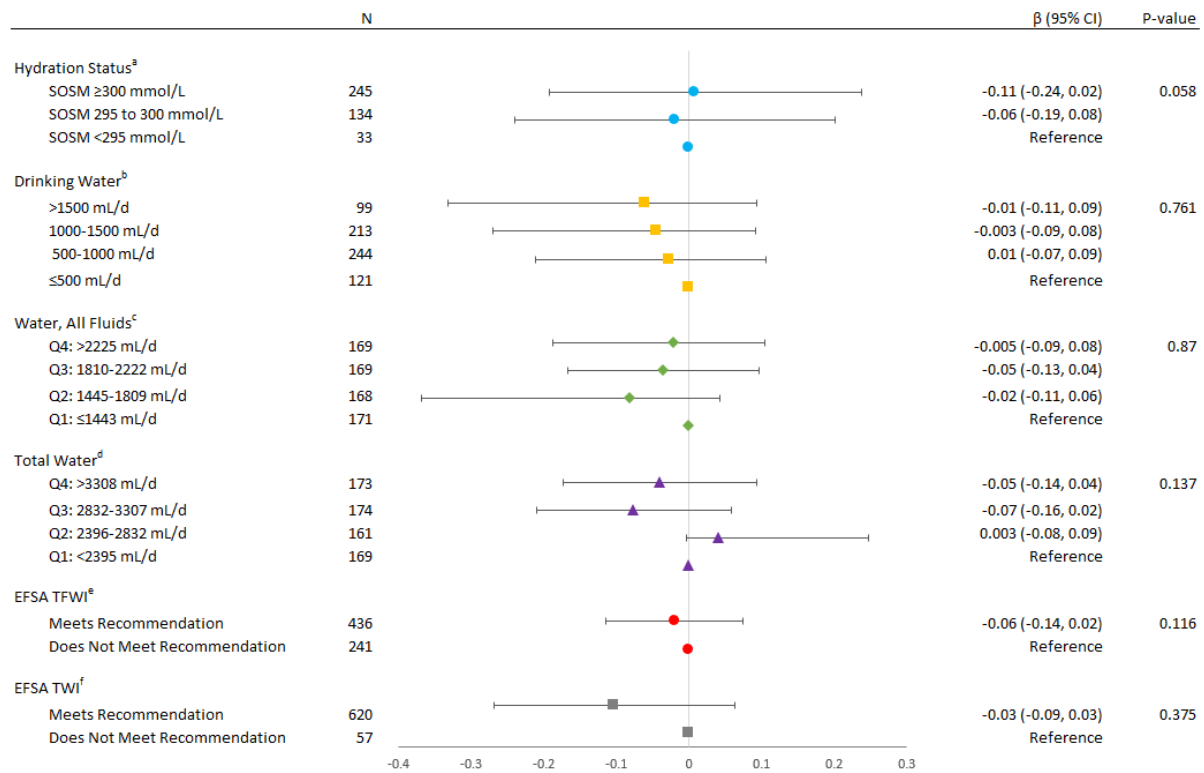


Linear regression models were adjusted for baseline covariates, including: baseline GCF score, age (years), sex, intervention PREDIMED-Plus randomized group, and participating center (≤ 100 , 100 to < 150 , 150 to < 200 , > 200 participants), body mass index (kg/m^2), educational level (primary, secondary or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), and physical activity ($\text{METs}/\text{min}/\text{day}$), 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).

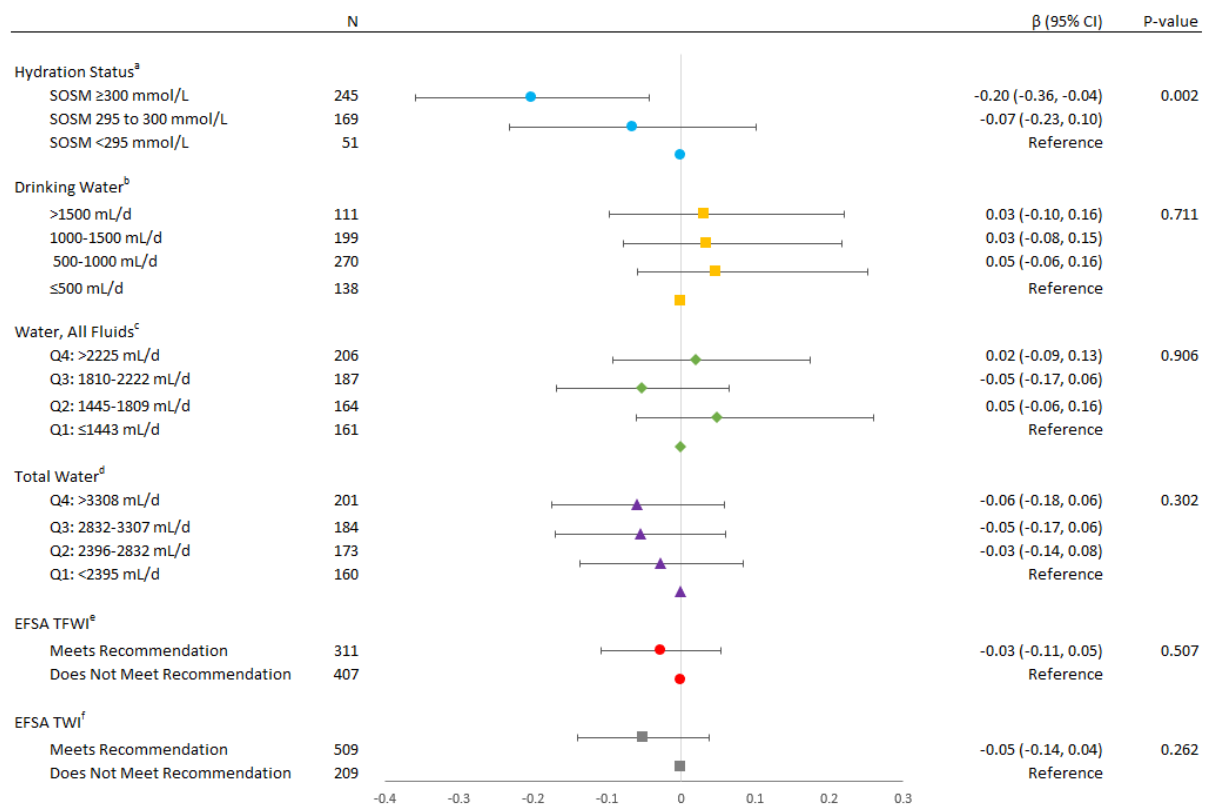
Beta represents changes in global cognitive function, expressed as z-scores, with each hydration or fluid intake component continuously.

Figure 3. Beta-coefficients and 95% CI for hydration status and water and fluid intakes categorically with 2-year changes in global cognitive function (z-scores) in women (A) and men (B).

A) Women



B) Men



Linear regression models were adjusted for baseline covariates, including: baseline GCF score, age (years), 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^2), educational level (primary, secondary or college), civil status (single, divorced or separated, married, widower), smoking habit (current, former, or never), and physical activity ($\text{METs}/\text{min}/\text{day}$), 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).

^aHydration Status refers to serum osmolarity, where dehydration, impending dehydration, and hydrated statuses were defined as $\text{SOSM} >300$, 295-300, and <295 mmol/L , respectively

^bDrinking Water refers to tap and bottled water intakes.

^cWater, All Fluids refers to tap and bottled water, plus water from other beverages and fluid food sources, such as soups and smoothies.

^dTotal Water refers to water from all fluids in addition to water present in food sources.

^eEFSA 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.

^fEFSA 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 osmolarity.