Web Material

The Associations of Dietary Copper With Cognitive Outcomes: The ARIC Study

Jingkai Wei, Kan Z. Gianattasio, Erin Bennett, James D. Stewart, Xiaohui Xu, Eun Sug Park, Richard L. Smith, Qi Ying, Eric A. Whitsel, Melinda C. Power

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Web Appendix 1. Ascertainment of dementia cases

ARIC uses two approaches to ascertain dementia: (1) in-person dementia ascertainment during visits, and (2) dementia surveillance, relying on telephone cognitive assessment, informant interview, and review of hospitalization records and death certificates. We describe each process in detail below.

In person dementia ascertainment. All ARIC participants who attended a study visit completed cognitive testing. For participants attending visit 5 or visit 6, ARIC participants with low cognitive test scores, evidence of substantial decline in global cognition from the prior visit, incomplete cognitive testing, and (at Visit 5 only) all participants with prior neuroimaging, as well as a random sample of other participants were referred to formal, in-person dementia ascertainment, including completion of the Clinical Dementia Rating (CDR), Neuropsychiatric Inventory (NPI), and Functional Activities Questionnaire (FAQ). Dementia status was determined by computer algorithm using information of cognitive tests and other screening tools, and then confirmed by expert review.

Dementia surveillance. For ARIC participants who did not attend study visits in person, dementia ascertainment efforts included assessment of cognitive function using the Telephone Interview for Cognitive Status-Modified (TICSm) at the time of Visit 5, or the Six Item Screener (SIS) during annual and semi-annual follow-up calls from Visit 5 forward, informant telephone interviews using a modified version of the CDR and the FAQ at the time of Visit 5 or the AD8 during annual and semi-annual follow-up calls from Visit 5 forward, as well as consideration of ICD-9 codes for dementia from hospitalization records or dementia codes on death certificates for deceased participants. Dementia status was determined based on application of cut-offs to available scores from the TICSm, SIS, CDR, FAQ and AD8, as well as hospitalization/death certificate data.

If available, dementia status is assigned based on the in person dementia ascertainment. For persons without in-person dementia ascertainment, dementia status is assigned based on dementia surveillance efforts, prioritized by strength of information (TICSm/SIS, CDR/FAQ/AD8, hospitalization codes, then death certificates). Date of onset for dementia was determined to be the earliest date associated with information indicating dementia.

Because of these different criteria of dementia, the ascertainment of dementia was available even if the participant missed follow-up visits.

Web Appendix 2: Methods of multiple imputation by chained equations (MICE)

The process of MICE involves specification of models for prediction of each variable with missing data. The main goal of MICE in our application is to impute test-specific z-scores at visit 5 and visit 6.

For persons who were alive at the time of each study visit, we imputed scores at the median of study visit dates among persons who attended the visit. For participants who died after less than 1 year after baseline (here, ARIC Visit 4), no imputation was conducted. For participants who between 1 year after visit 4 and less than 1 year after the date of visit 5, only z-scores at visit 5 were imputed, and the date associated with the imputed cognitive test score was set as 6 months prior to death. For participants who died 1 or more years after visit 5, z-scores were imputed at the median visit 5 visit date, and the date associated with the second imputed cognitive test score was set as 6 months prior to death.

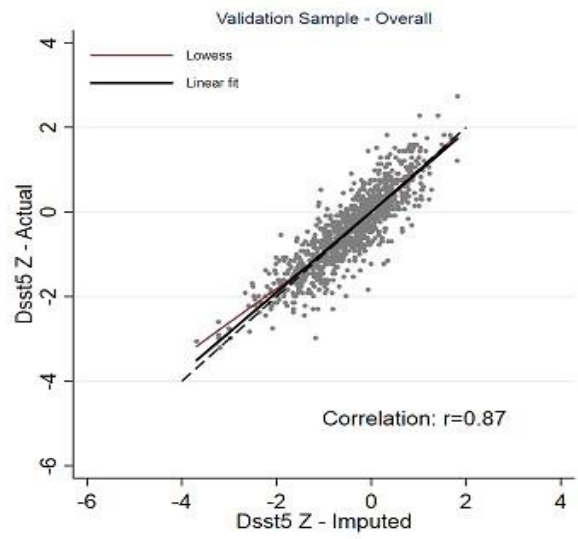
Scores at Visit 5 and Visit 6 which were imputed with models containing different covariates, since the covariates and available screening tools for z-scores visit 5 (CDR, TICs, MMSE) and visit 6 (SIS, AD8, MMSE) differed. Variables used to impute cognitive scores are provided in **Web Table 1**. For imputation of DWRT specifically, we applied winsorization to set the very small proportion of participants with DWRT equaling 0 or 1 to 2, and we truncated the imputed z-score of DWRT between -2.98 and 2.19, which were the minimum and maximum values for z-score of DWRT after winsorization. We used a burn in period of 50, and report final estimates based on combination of 5 imputations, using Rubin's rules.

To validate our MICE model, we first set to missing z-scores among a 20% random sample of participants who attended visit 5 and visit 6, respectively. We then compared the imputed z-scores with observed values (**Web Figure 1**). We also produced trace plots to confirm the stability of means and standard deviations of the imputed z-scores (**Web Figure 2**). Finally, we confirmed that the distribution of imputed z-scores by cognitive status and vital status matched expectations: specifically, the imputed z-scores at visit 6 were lower among those with participants with dementia compared to those without dementia, and lower for those who had died compared to those who were alive (**Web Figure 3**). The average imputed z-scores among all participants were much lower compared to average actual z-scores of complete cases and slightly lower compared to average imputed z-scores among those known to be alive at each study visit (**Web Table 2**).

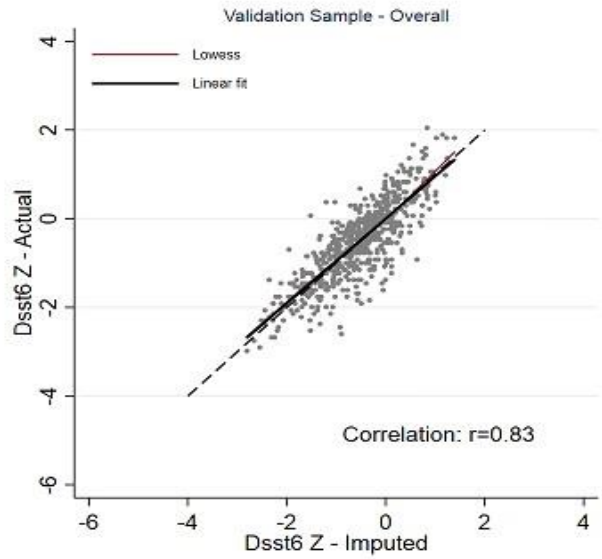
Web Table 1. Variables used to impute individual cognitive z-scores at visit 5 and visit 6

	For visit 5 z-scores	For visit 6 z-scores
Fixed variables	Sex, education, race-center, V1 income, APOE4	Sex, education, race-center, income, APOE4
Visit 1	Dietary copper, zinc, and iron intake from food, total calorie intake, saturated fat intake, dietary score	Dietary copper intake from food, total calorie intake, saturated fat intake, dietary score
Visit 2	Z-scores of DSST, DWRT and WFT	Z-scores of DSST, DWRT and WFT
Visit 3	Dietary copper, zinc, and iron intake from food and supplements, total calorie intake, saturated fat intake, dietary score	Dietary copper, zinc, and iron intake from food and supplements, total calorie intake, saturated fat intake, dietary score
Visit 4	Age, BMI, hypertension, diabetes, stroke, coronary heart disease, smoking, alcohol intake, z-scores of DSST, DWRT and WFT	Age, BMI, hypertension, diabetes, stroke, coronary heart disease, smoking, alcohol intake, z-scores of DSST, DWRT and WFT
V4 – V5 annual follow-up visits	Hospitalization, poor health, proxy	Hospitalization, poor health, proxy
Visit 5	BMI, hypertension, diabetes, stroke, coronary heart disease, smoking, alcohol intake, CDR, TICS, MMSE, time from V4 to V5, z-scores of DSST, DWRT and WFT, death by V5	BMI, hypertension, diabetes, stroke, coronary heart disease, smoking, alcohol intake, CDR, TICS, MMSE, time from V4 to V5, z-scores of DSST, DWRT and WFT, death by V5
V5 – V6 annual follow-up visits	Hospitalization, poor health	Hospitalization, poor health, SIS
Visit 6	Death by V6	MMSE, z-scores of DSST, DWRT, WFT, time between V4 and V6, time between V5 and V6, time between surveillance score and V6, death by V6
Interaction terms	V5 dementia status with V4 z-scores, V5 dementia status with V2 z-scores, V5 dementia status with education, V5 dementia status with race-center, V5 dementia status with V4 diabetes, V5 dementia status with V4 hypertension, V5 dementia status with CDR, V5 MMSE with education	V6 MMSE with V5 z-scores, V6 MMSE with education, copper intake with SIS, SIS with V5 z-scores, V6 dementia status with V5 z-scores, V6 dementia status with SIS, V6 dementia status with education, V6 dementia status with race-center, V6 dementia status with V4 diabetes, V6 dementia status with V4 hypertension, SIS with time from V5 to V6, SIS with time from surveillance score to V6

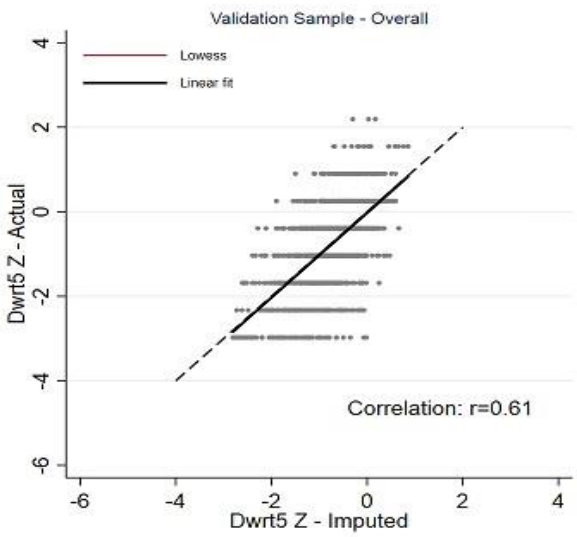
Web Figure 1. Comparison between imputed and observed (A1) DSST z-score at visit 5, (A2) DSST z-score at visit 6, (B1) DWRT z-score at visit 5, (B2) DWRT z-score at visit 6, (C1) WFT z-score at visit 5, (C2) WFT z-score at visit 6, (D1) Global z-score at visit 5, (D2) Global z-score at visit 6. *Global z-scores were calculated based on imputed z-scores of DSST, DWRT and WFT.



A1



A2



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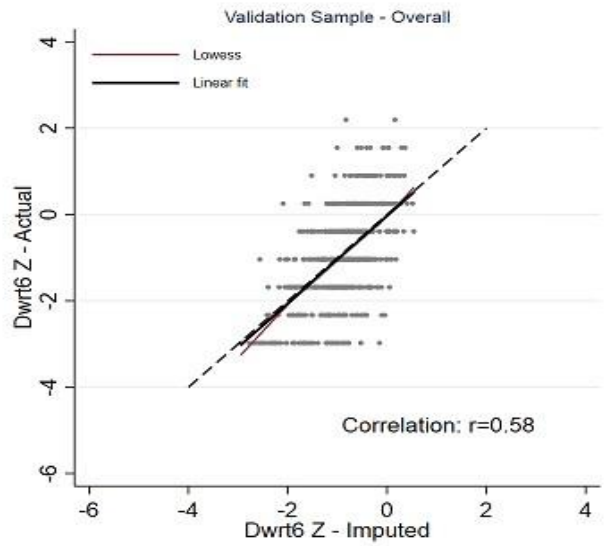

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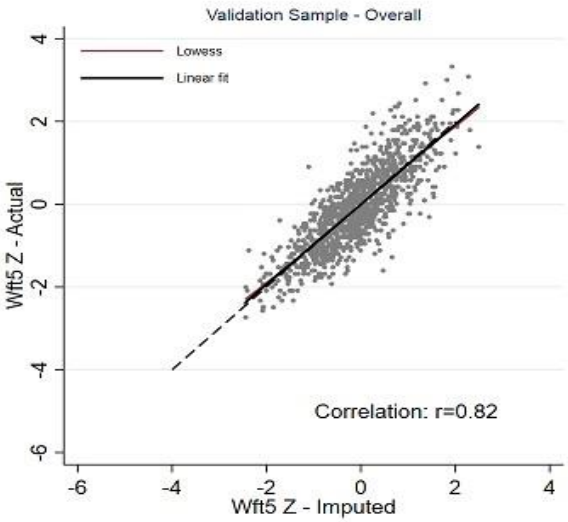
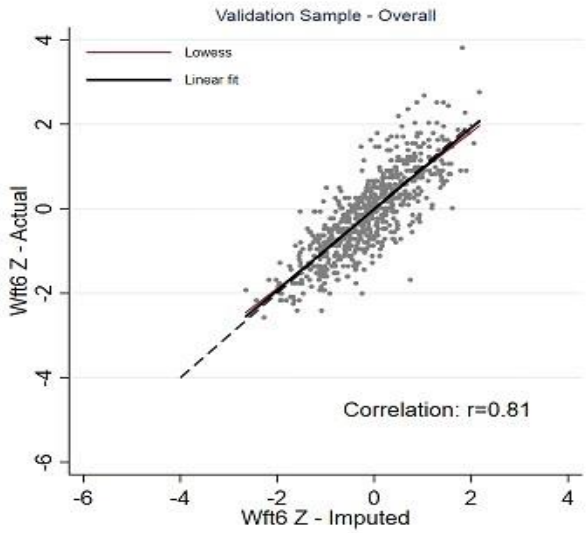
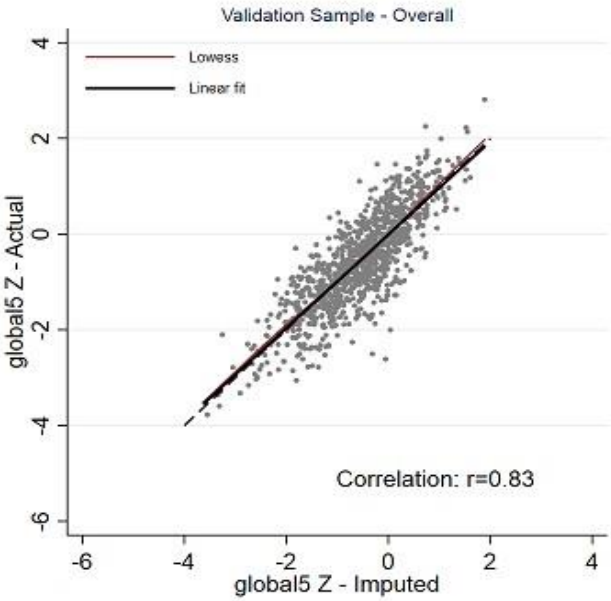

Validation Sample - Overall
Lowess
Linear fit
Wft5 Z - Actual
Wft5 Z - Imputed
Correlation: r=0.82

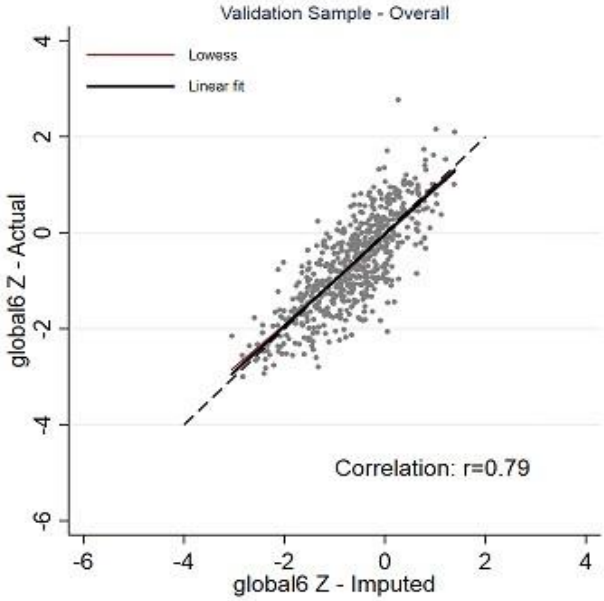
C1


Validation Sample - Overall
Lowess
Linear fit
Wft6 Z - Actual
Wft6 Z - Imputed
Correlation: r=0.81

C2

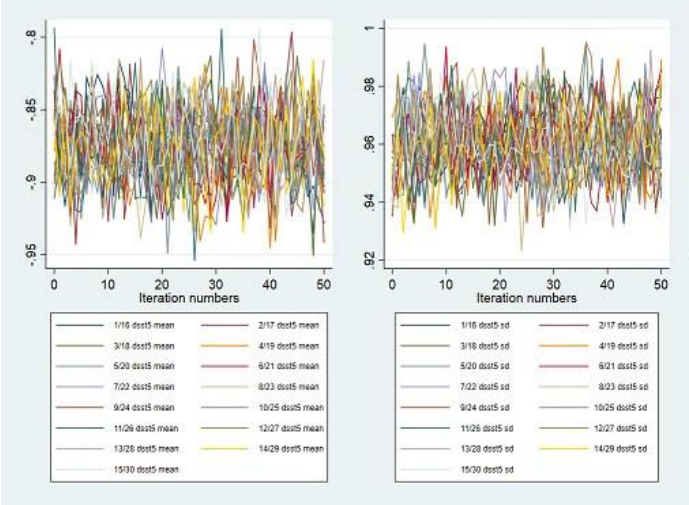

Validation Sample - Overall
Lowess
Linear fit
global5 Z - Actual
global5 Z - Imputed
Correlation: r=0.83

D1

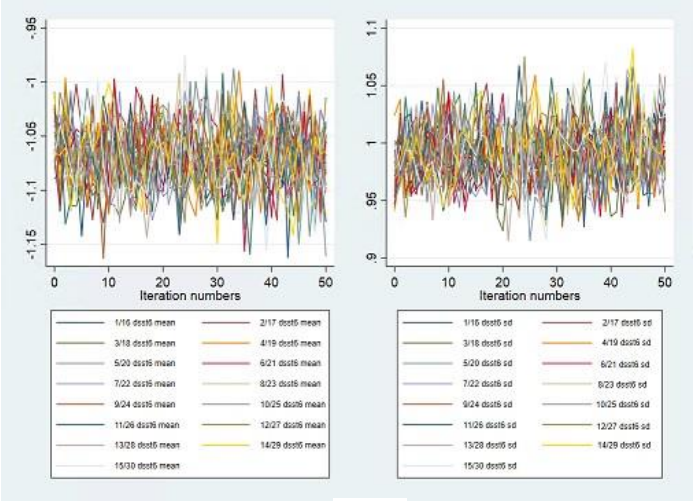

Validation Sample - Overall
Lowess
Linear fit
global6 Z - Actual
global6 Z - Imputed
Correlation: r=0.79

D2

Web Figure 2. Means and standard deviations of imputed (A1) DSST z-score at visit 5, (A2) DSST z-score at visit 6, (B1) DWRT z-score at visit 5, (B2) DWRT z-score at visit 6, (C1) WFT z-score at visit 5, (C2) WFT z-score at visit 6



A1



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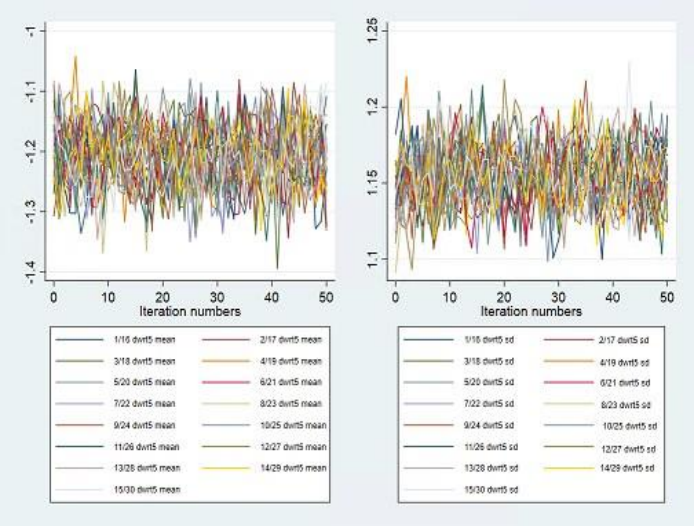

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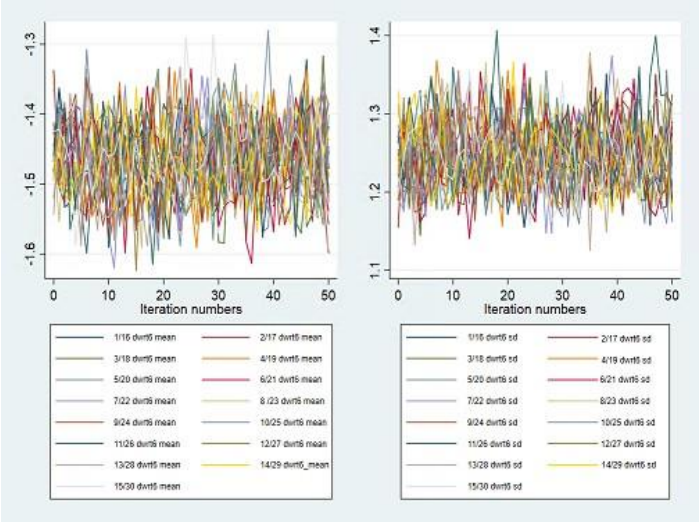

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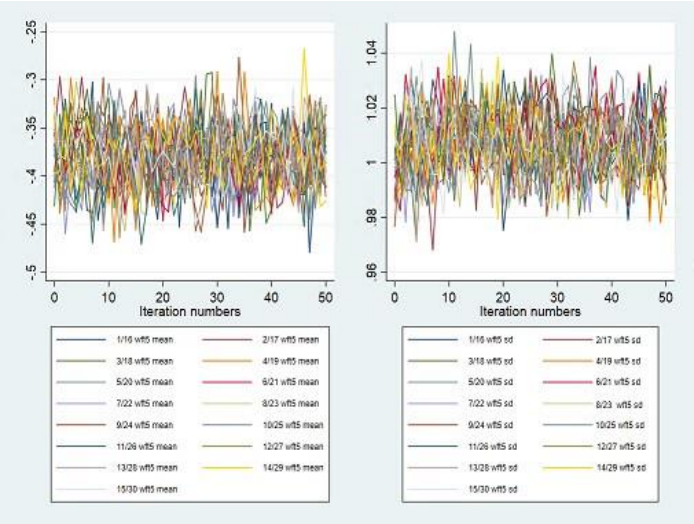
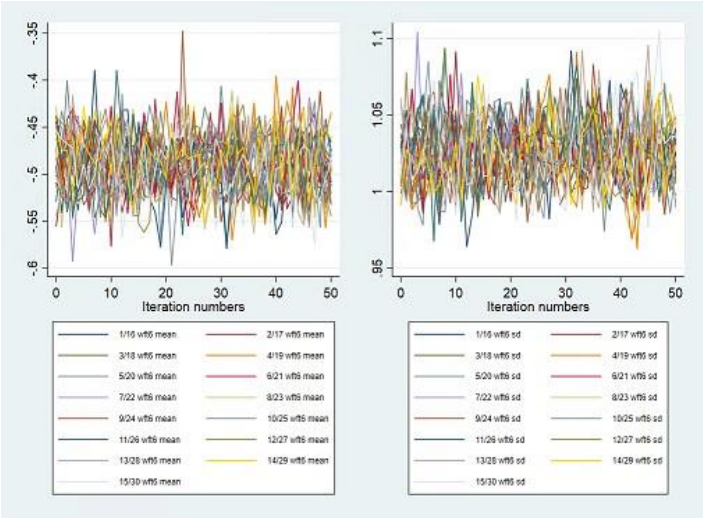


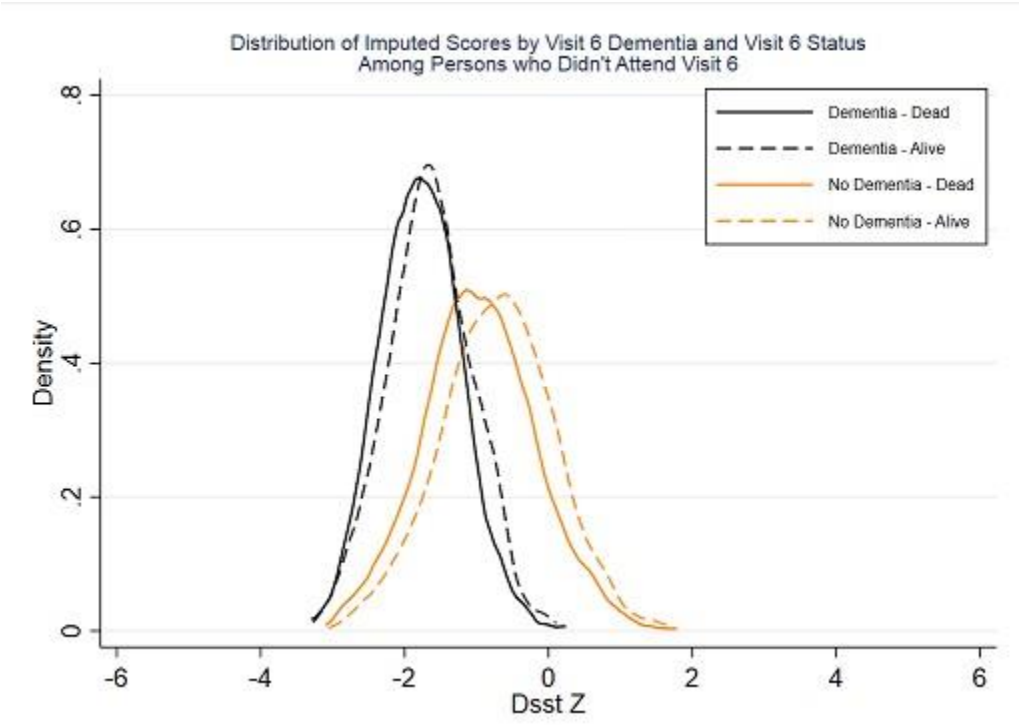
C1



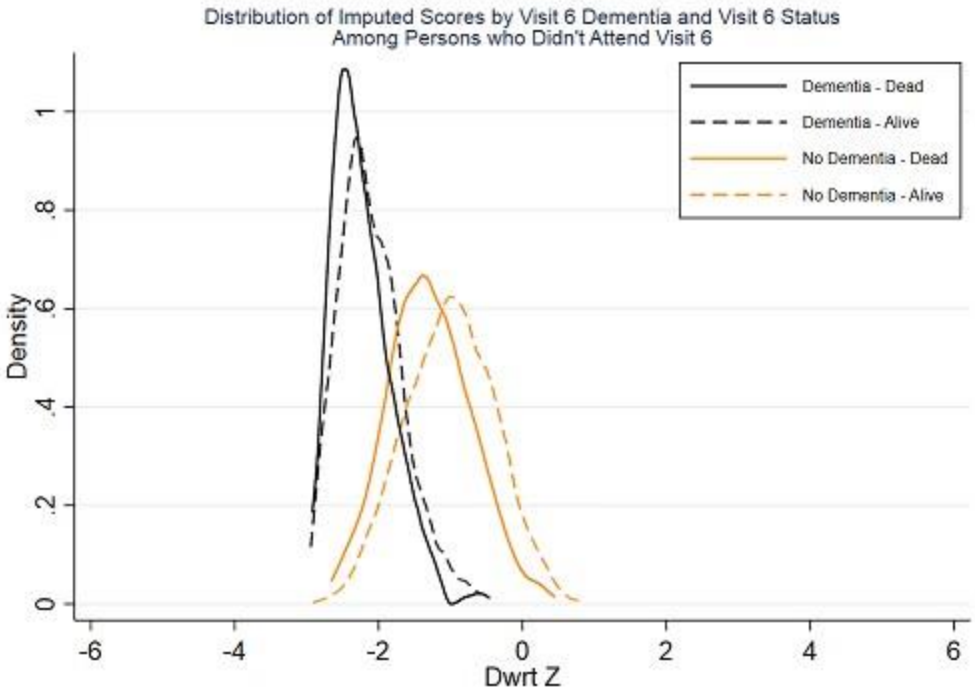
C2

Web Figure 3. Distribution imputed z-scores of (A) DSST, (B) DWRT, (C) WFT, (D) Global cognition at visit 6 by cognitive status and vital status.

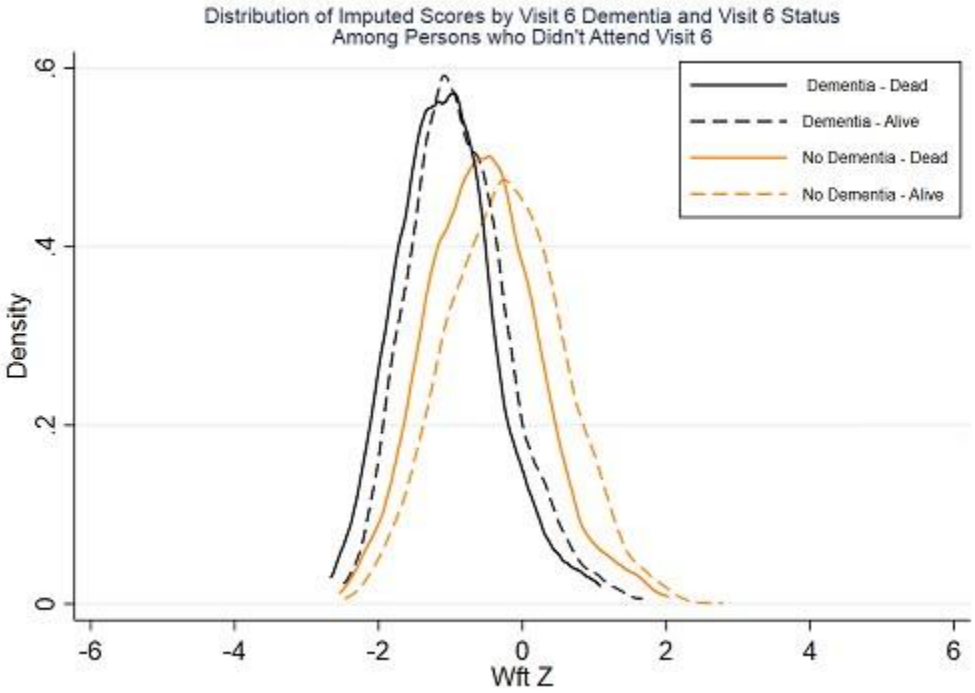
*Global z-scores were calculated based on imputed z-scores of DSST, DWRT and WFT.



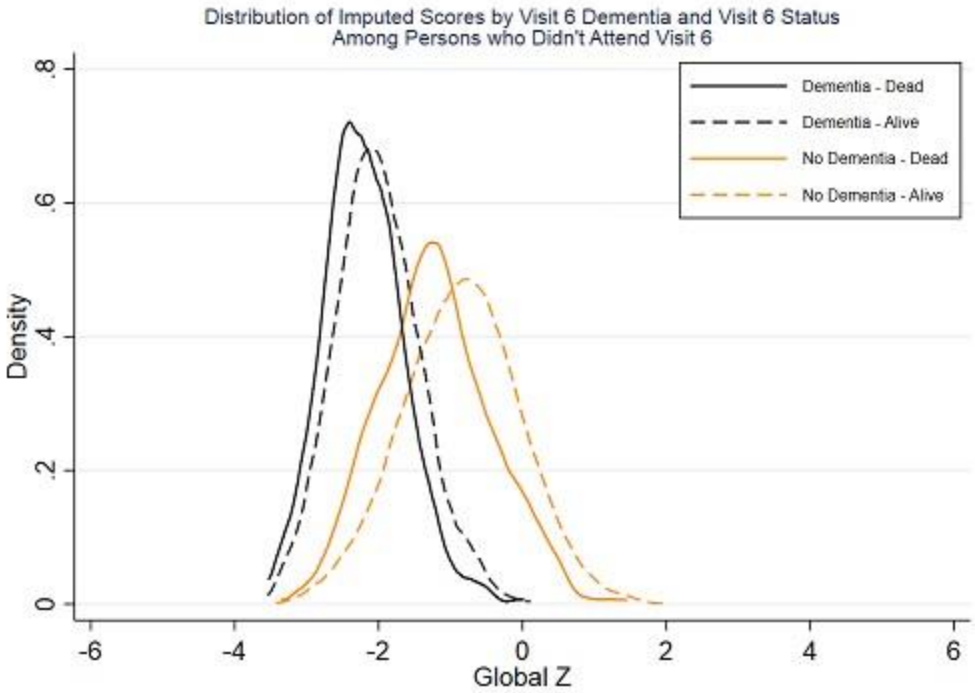
(A)


Distribution of Imputed Scores by Visit 6 Dementia and Visit 6 Status
Among Persons who Didn't Attend Visit 6
Dementia - Dead
Dementia - Alive
No Dementia - Dead
No Dementia - Alive
Density
0
.2
.4
.6
.8
1
-6
-4
-2
0
2
4
6
Dwrt Z

(B)


Distribution of Imputed Scores by Visit 6 Dementia and Visit 6 Status
Among Persons who Didn't Attend Visit 6
Dementia - Dead
Dementia - Alive
No Dementia - Dead
No Dementia - Alive
Density
0
.2
.4
.6
-6
-4
-2
0
2
4
6
Wft Z

(C)



(D)

Web Table 2. Number of incident cases of dementia by intake of dietary copper and saturated fat

	1st quartile of dietary copper		2nd quartile of dietary copper		3rd quartile of dietary copper		4th quartile of dietary copper		p-value for linear trend*
	Total N	Cases N (%)	Total N	Cases N (%)	Total N	Cases N (%)	Total N	Cases N (%)	
High saturate fat intake	115	15 (13.0)	398	55 (13.8)	969	147 (15.2)	1,077	193 (17.9)	0.02
Non-high saturate fat intake	2,447	462 (18.9)	2,145	419 (19.5)	1,623	283 (17.4)	1,476	288 (19.5)	0.87
Overall	2,562	477 (18.6)	2,543	474 (18.6)	2,592	430 (16.6)	2,553	481 (18.8)	0.68

*The p-value for linear trend was obtained with Chi-square test on quartiles of total dietary copper intake and incident dementia.

Web Table 3. Distribution of test-specific and global z-scores at visit 6 among complete and imputed cases

	DSST	DWRT	WFT	Global
Visit 5				
Without imputation	(n=5,294) -0.42±0.90 Range: -3.21, 2.73	(n=5,381) -0.84±1.12 Range: -2.98, 2.19	(n=5,354) -0.05±0.99 Range: -2.73, 3.73	(n=5,193) -0.54±1.00 Range: -3.77, 2.81
After imputation--alive only	(n=8,013) -0.60±0.93 Range: -3.95, 2.73	(n=8,013) -0.97±1.04 Range: -2.98, 2.19	(n=8,013) -0.16±0.97 Range: -3.28, 3.73	(n=8,013) -0.75±1.03 Range: -4.18, 2.81
After imputation –alive and dead	(n=10,206) -0.65±0.92 Range: -3.95, 2.73	(n=10,206) -1.01±0.99 Range: -2.98, 2.19	(n=10,206) -0.20±0.95 Range: -3.28, 3.73	(n=10,206) -0.81±1.01 Range: -4.18, 2.81
Visit 6				
Without imputation	(n=3,267) -0.53±0.88 Range: -3.36, 2.12	(n=3,349) -0.90±1.08 Range: -2.98, 2.19	(n=3,364) -0.10±0.99 Range: -2.65, 3.81	(n=3,212) -0.63±0.98 Range: -3.54, 2.77
After imputation--alive only	(n=6,552) -0.76±0.92 Range: -3.38, 2.31	(n=6,552) -1.09±0.99 Range: -2.98, 2.19	(n=6,552) -0.25±0.95 Range: -3.01, 3.81	(n=6,552) -0.91±1.01 Range: -3.71, 2.77
After imputation –alive and dead	(n=7,500) -0.84±0.94 Range: -3.88, 2.31	(n=7,500) -1.17±0.98 Range: -2.98, 2.19	(n=7,500) -0.32±0.96 Range: -3.01, 3.81	(n=7,500) -1.01±1.04 Range: -3.71, 2.77

Web Table 4. Association between dietary copper intake and 20-year cognitive decline among participants with no missing data on covariates or outcomes (n=9,510)

Global Z score				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.03 (-0.13, 0.07)	0.06 (-0.07, 0.18)	0.02 (-0.10, 0.15)
	Copper from supplements	0.02 (-0.01, 0.05)	**-0.04 (-0.07, -0.001)**	-0.02 (-0.06, 0.02)
	Total copper	-0.02 (-0.12, 0.09)	0.02 (-0.11, 0.15)	0.002 (-0.13, 0.13)
High saturate fat	Copper from food	0.001 (-0.13, 0.13)	0.09 (-0.07, 0.24)	0.09 (-0.06, 0.24)
	Copper from supplements	0.01 (-0.06, 0.08)	-0.04 (-0.13, 0.05)	-0.03 (-0.12, 0.06)
	Total copper	0.01 (-0.13, 0.15)	0.05 (-0.13, 0.22)	0.06 (-0.11, 0.23)
Non-high saturate fat	Copper from food	-0.05 (-0.16, 0.06)	0.04 (-0.10, 0.17)	-0.01 (-0.15, 0.12)
	Copper from supplements	0.02 (-0.02, 0.05)	-0.04 (-0.08, 0.003)	-0.02 (-0.06, 0.02)
	Total copper	-0.03 (-0.15, 0.08)	-0.001 (-0.14, 0.14)	-0.04 (-0.18, 0.10)
DSST				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	0.03 (-0.05, 0.11)	0.001 (-0.10, 0.10)	0.03 (-0.06, 0.13)
	Copper from supplements	-0.01 (-0.03, 0.02)	-0.03 (-0.06, 0.001)	**-0.03 (-0.06, -0.01)**
	Total copper	0.02 (-0.06, 0.11)	-0.03 (-0.13, 0.08)	-0.003 (-0.10, 0.10)
High saturate fat	Copper from food	0.07 (-0.03, 0.18)	0.04 (-0.09, 0.16)	0.11 (-0.01, 0.23)
	Copper from supplements	-0.005 (-0.06, 0.05)	0.02 (-0.05, 0.09)	0.01 (-0.05, 0.08)
	Total copper	0.07 (-0.04, 0.18)	0.05 (-0.08, 0.19)	0.12 (-0.01, 0.26)
Non-high saturate fat	Copper from food	0.01 (-0.08, 0.10)	-0.02 (-0.13, 0.08)	-0.02 (-0.12, 0.09)
	Copper from supplements	-0.01 (-0.03, 0.02)	**-0.04 (-0.07, -0.01)**	**-0.05 (-0.08, -0.01)**
	Total copper	-0.0002 (-0.09, 0.09)	-0.06 (-0.17, 0.05)	-0.06 (-0.17, 0.05)
DWRT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.02 (-0.17, 0.13)	0.18 (-0.02, 0.38)	0.16 (-0.02, 0.34)
	Copper from supplements	0.03 (-0.02, 0.07)	-0.05 (-0.11, 0.01)	-0.02 (-0.08, 0.03)
	Total copper	0.01 (-0.15, 0.17)	0.13 (-0.08, 0.33)	0.14 (-0.05, 0.33)
High saturate fat	Copper from food	0.02 (-0.18, 0.21)	0.23 (-0.02, 0.48)	**0.25 (0.02, 0.47)**
	Copper from supplements	0.01 (-0.09, 0.11)	-0.03 (-0.17, 0.11)	-0.02 (-0.15, 0.10)
	Total copper	0.03 (-0.19, 0.24)	0.20 (-0.07, 0.47)	0.23 (-0.02, 0.48)
Non-high saturate fat	Copper from food	-0.03 (-0.20, 0.13)	0.15 (-0.07, 0.36)	0.11 (-0.09, 0.31)
	Copper from supplements	0.03 (-0.02, 0.08)	-0.06 (-0.12, 0.01)	-0.03 (-0.09, 0.03)
	Total copper	-0.003 (-0.18, 0.17)	0.09 (-0.14, 0.31)	0.09 (-0.12, 0.29)
WFT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.10 (-0.19, 0.002)	-0.05 (-0.17, 0.07)	**-0.14 (-0.26, -0.03)**
	Copper from supplements	0.005 (-0.02, 0.03)	-0.01 (-0.05, 0.02)	-0.01 (-0.04, 0.03)
	Total copper	-0.09 (-0.19, 0.01)	-0.06 (-0.18, 0.06)	**-0.15 (-0.27, -0.03)**
High saturate fat	Copper from food	-0.08 (-0.20, 0.05)	-0.04 (-0.19, 0.11)	-0.11 (-0.26, 0.03)
	Copper from supplements	-0.02 (-0.09, 0.05)	-0.07 (-0.16, 0.01)	**-0.09 (-0.17, -0.01)**
	Total copper	-0.09 (-0.23, 0.04)	-0.11 (-0.27, 0.05)	**-0.21 (-0.36 -0.05)**
Non-high saturate fat	Copper from food	-0.10 (-0.21, 0.002)	-0.05 (-0.18, 0.08)	**-0.15 (-0.27, -0.02)**
	Copper from supplements	0.01 (-0.02, 0.04)	0.001 (-0.04, 0.04)	0.01 (-0.03, 0.05)
	Total copper	-0.09 (-0.20, 0.02)	-0.04 (-0.18, 0.09)	**-0.14 (-0.27, -0.01)**

Mixed models were adjusted for age, sex, race-center, APOE4, education, BMI, smoking, alcohol drinking, total calorie intake, saturated fat intake, zinc intake, iron intake, dietary patterns, and their interactions with time spline terms.

Web Table 5. Association between dietary copper intake and 20-year cognitive decline with MICE imputation for missing covariates only (n=10,269)

Global Z score				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.03 (-0.13, 0.07)	0.05 (-0.07, 0.17)	0.02 (-0.10, 0.15)
	Copper from supplements	0.02 (-0.01, 0.05)	**-0.04 (-0.08, -0.003)**	-0.02 (-0.05, 0.02)
	Total copper	-0.01 (-0.11, 0.09)	0.01 (-0.11, 0.14)	0.01 (-0.12, 0.13)
High saturate fat	Copper from food	0.0002 (-0.12, 0.12)	0.09 (-0.06, 0.24)	0.09 (-0.06, 0.24)
	Copper from supplements	0.01 (-0.05, 0.08)	-0.04 (-0.12, 0.05)	-0.02 (-0.10, 0.06)
	Total copper	0.01 (-0.12, 0.15)	0.05 (-0.12, 0.22)	0.07 (-0.10, 0.24)
Non-high saturate fat	Copper from food	-0.04 (-0.15, 0.06)	0.03 (-0.10, 0.16)	-0.01 (-0.14, 0.12)
	Copper from supplements	0.02 (-0.01, 0.05)	-0.04 (-0.08, 0.0003)	-0.02 (-0.06, 0.02)
	Total copper	-0.02 (-0.13, 0.09)	-0.01 (-0.15, 0.13)	-0.03 (-0.17, 0.11)
DSST				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	0.04 (-0.04, 0.12)	-0.002 (-0.10, 0.10)	0.04 (-0.06, 0.13)
	Copper from supplements	-0.004 (-0.03, 0.02)	**-0.03 (-0.06, -0.004)**	**-0.04 (-0.06, -0.01)**
	Total copper	0.04 (-0.05, 0.12)	-0.03 (-0.14, 0.07)	0.001 (-0.10, 0.10)
High saturate fat	Copper from food	0.07 (-0.03, 0.17)	0.04 (-0.08, 0.16)	0.11 (-0.01, 0.23)
	Copper from supplements	0.001 (-0.05, 0.06)	0.004 (-0.06, 0.07)	0.01 (-0.06, 0.07)
	Total copper	0.07 (-0.04, 0.18)	0.05 (-0.09, 0.18)	0.12 (-0.01, 0.25)
Non-high saturate fat	Copper from food	0.02 (-0.06, 0.11)	-0.03 (-0.14, 0.07)	-0.01 (-0.11, 0.09)
	Copper from supplements	-0.01 (-0.03, 0.02)	**-0.04 (-0.07, -0.01)**	**-0.05 (-0.08, -0.02)**
	Total copper	0.02 (-0.07, 0.11)	-0.07 (-0.18, 0.04)	-0.06 (-0.16, 0.05)
DWRT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.02 (-0.17, 0.13)	0.16 (-0.04, 0.35)	0.14 (-0.04, 0.32)
	Copper from supplements	0.04 (-0.01, 0.08)	-0.05 (-0.11, 0.01)	-0.02 (-0.07, 0.04)
	Total copper	0.02 (-0.14, 0.18)	0.11 (-0.09, 0.31)	0.13 (-0.06, 0.31)
High saturate fat	Copper from food	0.02 (-0.17, 0.21)	0.22 (-0.03, 0.46)	**0.23 (0.01, 0.45)**
	Copper from supplements	0.01 (-0.09, 0.12)	-0.02 (-0.16, 0.11)	-0.01 (-0.13, 0.11)
	Total copper	0.03 (-0.18, 0.24)	0.19 (-0.07, 0.46)	0.22 (-0.02, 0.46)
Non-high saturate fat	Copper from food	-0.03 (-0.19, 0.13)	0.12 (-0.09, 0.33)	0.09 (-0.10, 0.29)
	Copper from supplements	0.04 (-0.01, 0.09)	-0.06 (-0.12, 0.01)	-0.02 (-0.08, 0.04)
	Total copper	0.01 (-0.16, 0.18)	0.06 (-0.16, 0.28)	0.08 (-0.13, 0.28)
WFT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.09 (-0.19, 0.003)	-0.04 (-0.16, 0.08)	**-0.13 (-0.24, -0.02)**
	Copper from supplements	0.003 (-0.02, 0.03)	-0.01 (-0.05, 0.02)	-0.01 (-0.04, 0.02)
	Total copper	-0.09 (-0.19, 0.01)	-0.05 (-0.17, 0.07)	**-0.14 (-0.26, -0.03)**
High saturate fat	Copper from food	-0.08 (-0.20, 0.05)	-0.04 (-0.18, 0.11)	-0.11 (-0.25, 0.03)
	Copper from supplements	-0.02 (-0.09, 0.04)	-0.05 (-0.13, 0.03)	**-0.08 (-0.15, -0.001)**
	Total copper	-0.10 (-0.23, 0.03)	-0.09 (-0.25, 0.07)	**-0.19 (-0.34, -0.04)**
Non-high saturate fat	Copper from food	-0.10 (-0.20, 0.01)	-0.04 (-0.17, 0.09)	**-0.14 (-0.26, -0.02)**
	Copper from supplements	0.01 (-0.02, 0.04)	-0.002 (-0.04, 0.04)	0.01 (-0.03, 0.04)
	Total copper	-0.09 (-0.19, 0.02)	-0.04 (-0.17, 0.09)	**-0.13 (-0.25, -0.003)**

Mixed models were adjusted for age, sex, race-center, APOE4, education, BMI, smoking, alcohol drinking, total calorie intake, saturated fat intake, zinc intake, iron intake, dietary patterns, and their interactions with time spline terms.

Web Table 6. Association between dietary copper intake and 20-year cognitive decline, with MICE imputation for missing covariates and outcomes for participants who are alive at each visit (n=10,269)

Global Z score				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.04 (-0.13, 0.05)	0.02 (-0.13, 0.17)	-0.02 (-0.15, 0.12)
	Copper from supplements	0.02 (-0.01, 0.04)	**-0.05 (-0.08, -0.01)**	-0.03 (-0.06, 0.005)
	Total copper	-0.02 (-0.11, 0.07)	-0.03 (-0.17, 0.12)	-0.05 (-0.18, 0.09)
High saturate fat	Copper from food	0.01 (-0.10, 0.12)	0.04 (-0.12, 0.20)	0.05 (-0.10, 0.20)
	Copper from supplements	0.002 (-0.05, 0.06)	-0.05 (-0.12, 0.03)	-0.04 (-0.12, 0.03)
	Total copper	0.01 (-0.11, 0.13)	-0.004 (-0.18, 0.17)	0.01 (-0.16, 0.18)
Non-high saturate fat	Copper from food	-0.06 (-0.16, 0.03)	0.01 (-0.15, 0.17)	-0.05 (-0.20, 0.09)
	Copper from supplements	0.02 (-0.01, 0.05)	**-0.05 (-0.08, -0.01)**	-0.03 (-0.06, 0.01)
	Total copper	-0.04 (-0.14, 0.06)	-0.04 (-0.19, 0.11)	-0.08 (-0.22, 0.06)
DSST				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	0.02 (-0.06, 0.10)	-0.01 (-0.10, 0.08)	0.02 (-0.08, 0.12)
	Copper from supplements	-0.01 (-0.03, 0.02)	**-0.05 (-0.07, -0.02)**	**-0.05 (-0.09, -0.02)**
	Total copper	0.02 (-0.06, 0.10)	-0.05 (-0.15, 0.04)	-0.04 (-0.14, 0.06)
High saturate fat	Copper from food	0.06 (-0.04, 0.16)	-0.002 (-0.11, 0.11)	0.06 (-0.06, 0.18)
	Copper from supplements	0.004 (-0.05, 0.06)	-0.04 (-0.10, 0.03)	-0.03 (-0.10, 0.03)
	Total copper	0.07 (-0.03, 0.17)	-0.04 (-0.16, 0.08)	0.03 (-0.11, 0.16)
Non-high saturate fat	Copper from food	0.002 (-0.08, 0.09)	-0.01 (-0.11, 0.09)	-0.01 (-0.11, 0.09)
	Copper from supplements	-0.01 (-0.03, 0.02)	**-0.05 (-0.08, -0.02)**	**-0.06 (-0.10, -0.02)**
	Total copper	-0.01 (-0.09, 0.08)	-0.06 (-0.16, 0.04)	-0.07 (-0.17, 0.03)
DWRT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.02 (-0.15, 0.12)	0.10 (-0.13, 0.33)	0.09 (-0.11, 0.28)
	Copper from supplements	0.04 (-0.01, 0.08)	-0.04 (-0.09, 0.002)	-0.01 (-0.06, 0.04)
	Total copper	0.02 (-0.12, 0.16)	0.06 (-0.17, 0.28)	0.08 (-0.12, 0.28)
High saturate fat	Copper from food	0.04 (-0.14, 0.21)	0.16 (-0.10, 0.41)	0.19 (-0.02, 0.41)
	Copper from supplements	0.01 (-0.08, 0.10)	-0.04 (-0.15, 0.08)	-0.03 (-0.14, 0.09)
	Total copper	0.05 (-0.14, 0.24)	0.12 (-0.16, 0.40)	0.17 (-0.08, 0.41)
Non-high saturate fat	Copper from food	-0.04 (-0.19, 0.11)	0.07 (-0.18, 0.32)	0.03 (-0.18, 0.25)
	Copper from supplements	0.04 (-0.01, 0.09)	-0.05 (-0.10, 0.01)	-0.004 (-0.06, 0.05)
	Total copper	0.004 (-0.15, 0.16)	0.03 (-0.22, 0.27)	0.03 (-0.19, 0.25)
WFT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.08 (-0.17, 0.02)	-0.05 (-0.15, 0.05)	**-0.12 (-0.22, 0.03)**
	Copper from supplements	0.003 (-0.02, 0.03)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)
	Total copper	-0.07 (-0.17, 0.02)	-0.06 (-0.16, 0.04)	**-0.13 (-0.24, -0.02)**
High saturate fat	Copper from food	-0.05 (-0.17, 0.06)	-0.04 (-0.17, 0.08)	-0.10 (-0.23, 0.03)
	Copper from supplements	-0.02 (-0.08, 0.04)	-0.03 (-0.09, 0.03)	-0.04 (-0.10, 0.01)
	Total copper	-0.07 (-0.20, 0.06)	-0.07 (-0.21, 0.06)	**-0.14 (-0.28, -0.01)**
Non-high saturate fat	Copper from food	-0.08 (-0.18, 0.01)	-0.05 (-0.16, 0.06)	**-0.13 (-0.24, -0.03)**
	Copper from supplements	0.01 (-0.02, 0.04)	-0.004 (-0.04, 0.03)	0.004 (-0.03, 0.04)
	Total copper	-0.08 (-0.18, 0.03)	-0.05 (-0.16, 0.06)	**-0.13 (-0.24, -0.02)**

Mixed models were adjusted for age, sex, race-center, APOE4, education, BMI, smoking, alcohol drinking, total calorie intake, saturated fat intake, zinc intake, iron intake, dietary patterns, and their interactions with time spline terms.

Web Table 7. Association between dietary copper intake and 20-year cognitive decline, with MICE imputation for covariates and outcomes for all participants, without adjustment for dietary components (zinc, iron, diet score) in mixed models analyses (n=10,269)

Global Z score				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.02 (-0.10, 0.07)	0.004 (-0.16, 0.17)	-0.01 (-0.16, 0.14)
	Copper from supplements	0.02 (-0.01, 0.04)	**-0.05 (-0.08, -0.02)**	-0.03 (-0.07, 0.001)
	Total copper	-0.001 (-0.09, 0.08)	-0.04 (-0.21, 0.12)	-0.05 (-0.20, 0.11)
High saturate fat	Copper from food	0.02 (-0.09, 0.13)	0.03 (-0.15, 0.20)	0.05 (-0.10, 0.20)
	Copper from supplements	0.001 (-0.05, 0.05)	-0.05 (-0.13, 0.03)	-0.05 (-0.13, 0.03)
	Total copper	0.02 (-0.10, 0.14)	-0.02 (-0.22, 0.17)	-0.002 (-0.17, 0.17)
Non-high saturate fat	Copper from food	-0.03 (-0.12, 0.06)	-0.01 (-0.18, 0.16)	-0.04 (-0.20, 0.12)
	Copper from supplements	0.02 (-0.01, 0.05)	**-0.05 (-0.09, -0.01)**	-0.03 (-0.06, 0.01)
	Total copper	-0.01 (-0.11, 0.08)	-0.06 (-0.22, 0.11)	-0.07 (-0.24, 0.10)
DSST				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	0.03 (-0.03, 0.10)	-0.02 (-0.10, 0.06)	0.01 (-0.08, 0.11)
	Copper from supplements	-0.01 (-0.03, 0.02)	**-0.05 (-0.08, -0.02)**	**-0.06 (-0.10, -0.02)**
	Total copper	0.03 (-0.04, 0.09)	-0.07 (-0.16, 0.01)	-0.05 (-0.14, 0.05)
High saturate fat	Copper from food	0.07 (-0.02, 0.16)	-0.02 (-0.12, 0.09)	0.05 (-0.07, 0.17)
	Copper from supplements	-0.002 (-0.05, 0.05)	-0.04 (-0.10, 0.02)	-0.04 (-0.10, 0.02)
	Total copper	0.07 (-0.03, 0.16)	-0.06 (-0.18, 0.06)	0.01 (-0.12, 0.14)
Non-high saturate fat	Copper from food	0.02 (-0.06, 0.09)	-0.02 (-0.11, 0.07)	-0.01 (-0.10, 0.09)
	Copper from supplements	-0.01 (-0.04, 0.02)	**-0.05 (-0.09, -0.02)**	**-0.06 (-0.10, -0.02)**
	Total copper	0.01 (-0.07, 0.08)	-0.08 (-0.16, 0.01)	-0.07 (-0.16, 0.02)
DWRT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.01 (-0.13, 0.11)	0.10 (-0.14, 0.33)	0.09 (-0.11, 0.29)
	Copper from supplements	0.04 (-0.01, 0.08)	**-0.05 (-0.09, -0.003)**	-0.01 (-0.06, 0.04)
	Total copper	0.03 (-0.09, 0.16)	0.05 (-0.19, 0.28)	0.08 (-0.13, 0.29)
High saturate fat	Copper from food	0.03 (-0.14, 0.21)	0.15 (-0.11, 0.41)	0.19 (-0.02, 0.39)
	Copper from supplements	0.01 (-0.08, 0.10)	-0.04 (-0.16, 0.08)	-0.03 (-0.15, 0.09)
	Total copper	0.05 (-0.14, 0.23)	0.11 (-0.18, 0.40)	0.16 (-0.09, 0.40)
Non-high saturate fat	Copper from food	-0.02 (-0.15, 0.10)	0.06 (-0.18, 0.31)	0.04 (-0.20, 0.27)
	Copper from supplements	0.04 (-0.01, 0.10)	-0.05 (-0.10, 0.001)	-0.01 (-0.06, 0.04)
	Total copper	0.02 (-0.12, 0.16)	0.01 (-0.23, 0.26)	0.03 (-0.20, 0.27)
WFT				
		1-15 years β (95% CI)	16-20 years β (95% CI)	1-20 years β (95% CI)
Overall	Copper from food	-0.06 (-0.14, 0.03)	-0.07 (-0.19, 0.06)	**-0.13 (-0.24, -0.01)**
	Copper from supplements	0.002 (-0.02, 0.03)	-0.01 (-0.04, 0.02)	-0.01 (-0.03, 0.02)
	Total copper	-0.06 (-0.15, 0.03)	-0.08 (-0.20, 0.05)	**-0.13 (-0.24, -0.02)**
High saturate fat	Copper from food	-0.05 (-0.15, 0.05)	-0.06 (-0.21, 0.08)	-0.11 (-0.25, 0.03)
	Copper from supplements	-0.01 (-0.07, 0.05)	-0.03 (-0.09, 0.03)	-0.04 (-0.10, 0.02)
	Total copper	-0.06 (-0.17, 0.06)	-0.09 (-0.25, 0.07)	**-0.15 (-0.29, -0.02)**
Non-high saturate fat	Copper from food	-0.06 (-0.16, 0.03)	-0.07 (-0.19, 0.06)	**-0.13 (-0.25, -0.01)**
	Copper from supplements	0.01 (-0.02, 0.03)	-0.005 (-0.04, 0.03)	0.001 (-0.03, 0.03)
	Total copper	-0.06 (-0.16, 0.04)	-0.07 (-0.20, 0.06)	**-0.13 (-0.25, -0.01)**

Mixed models were adjusted for age, sex, race-center, APOE4, education, BMI, smoking, alcohol drinking, total calorie intake, saturated fat intake, and their interactions with time spline terms.