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The Associations of Dietary Copper With Cognitive Outcomes

The ARIC Study

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

* Correspondence to Dr. Jingkai Wei, Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, 915 Greene Street, Columbia, SC 29208 (e-mail: jwei@mailbox.sc.edu).

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Dietary copper intake may be associated with cognitive decline and dementia. We used data from 10,269 participants of the Atherosclerosis Risks in Communities Study to study the associations of dietary copper intake with 20-year cognitive decline and incident dementia. Dietary copper intake from food and supplements was quantified using food frequency questionnaires. Cognition was assessed using 3 cognitive tests at study visits; dementia was ascertained at study visits and via surveillance. Multiple imputation by chained equations was applied to account for the missing information of cognitive function during follow-up. Survival analysis with parametric models and mixed-effect models were used to estimate the associations for incident dementia and cognitive decline, respectively. During 20 years of follow-up (1996–1998 to 2016–2017), 1,862 incident cases of dementia occurred. Higher intake of dietary copper from food was associated with higher risk of incident dementia among those with high intake of saturated fat (hazard ratio = 1.49, 95% confidence interval: 1.04, 1.95). Higher intake of dietary copper from food was associated with greater decline in language overall (beta = −0.12, 95% confidence interval: −0.23, −0.02). Therefore, a diet high in copper, particularly when combined with a diet high in saturated fat, may increase the risk of cognitive impairment.

cognitive decline; copper; dementia; diet; multiple imputation; saturated fat

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; DSST, Digit Symbol Substitution Test; DWRT, Delayed Word Recall Test; FFQ, food frequency questionnaire; WFT, Word Fluency Test.

Copper is an essential nutrient for the human body. It is involved in various biological processes, including iron metabolism, antioxidant defense, neuropeptide synthesis, and immune function (1). Serious health issues may also occur due to acute excess of copper, such as Wilson disease and axonal neuropathy (2).

In vitro and in vivo studies suggest that copper may also be involved in Alzheimer disease pathogenesis. Copper binds in vivo with the peptide β-amyloid, accelerating its aggregation and formation of neurotoxic plaque, a pathologic hallmark of Alzheimer disease (3). Similarly, copper binds tau peptides and promotes aggregation of R2 and R3 peptides, which are involved in the formation of neurofibrillary tangles, another pathologic hallmark of Alzheimer disease (4, 5). Copper may also combine with apolipoprotein E and potentiate deposition of β-amyloid (6). Several small cross-sectional and longitudinal epidemiologic studies also suggest higher serum or free copper is associated with worse cognitive outcomes (7–10).

High cholesterol, particularly in midlife, is associated with cognitive decline and higher risk of dementia (11–14). Interestingly, laboratory and animal-based studies suggest that the combination of high dietary copper intake and high cholesterol intake promotes Alzheimer disease pathogenesis (15–17). This dietary copper–cholesterol interaction is supported in a large-scale epidemiologic study on dietary copper and cognitive outcomes. In the Chicago Health and Aging Project (CHAP), Morris et al. (18) found that higher dietary copper intake is associated with faster 6-year cognitive decline among subjects with high intake of saturated fats and

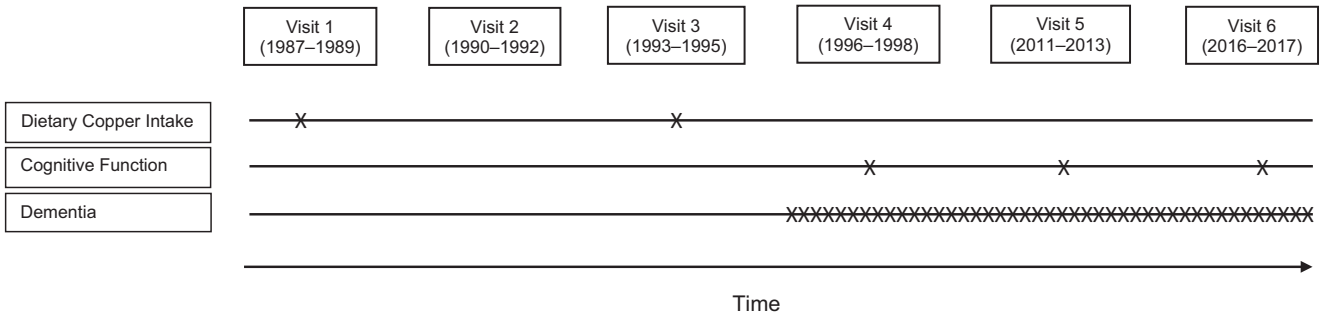

Figure 1. Timeline for assessments of dietary copper intake (visits 1 and 3), cognitive function (visits 4, 5, and 6), and incident dementia (from visit 4) in the Atherosclerosis Risk in Communities study, United States, 1987–2017.

trans fatty acids, among older adults. However, the follow-up period was relatively short, which raises concerns about reverse causation. Also, as the prodromal period of dementia persists for years to decades from midlife, exposures in midlife may be more relevant than exposures in late life. In addition, this study did not consider the impact of dietary copper on risk of dementia or on domain-specific cognitive change.

Thus, our objective was to examine the relationship of midlife dietary copper intake with 20-year cognitive decline and incident dementia in data from the Atherosclerosis Risk in Communities (ARIC) Study, overall and within those with high vs. low saturated fat intake.

METHODS

Study design and population

The study is based in the Atherosclerosis Risk in Communities (ARIC) cohort. A total of 15,792 participants aged 45–64 years were examined in 1987–1989, sampled from 4 communities in the United States (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland) (19). We included 10,406 ARIC participants with information on dietary copper intake at visit 1 (1987–1989) and visit 3 (1993–1995) and baseline cognitive data at visit 4 (1996–1998) (Figure 1). We further excluded otherwise eligible participants who are Asian or Native Americans, Black participants in Maryland and Minnesota due to small numbers ($n = 69$), participants who reported implausible total caloric intake (women with total energy intake <500 calories/day or >3,500 calories/day, men with total energy intake <700 calories/day or >4500 calories/day) ($n = 55$), and participants who were missing information on education ($n = 13$) from all analyses. A total of 10,269 participants remained in our analysis. Informed consent was obtained from participants at each visit, and the study protocols were approved by institutional review boards at collaborating institutions.

Dietary copper intake

Dietary intake was assessed in the full ARIC sample at visits 1 and 3 using an interviewer-administered, 66-item food frequency questionnaire (FFQ) adapted from the 61-item FFQ developed by Willett et al. (20). Participants were asked to report the frequency of intake of specific food items. The estimated amount of nutrient intake, including copper, was then calculated from nutrient values of foods provided by the Willett group. The intake of copper, zinc, and iron measured with Willett has been validated with 7-day dietary records (energy-adjusted intraclass correlation coefficients = 0.60, 0.49, and 0.54, respectively) (21). In addition to the FFQ, a vitamin survey was conducted at visit 3, collecting information about intake of multiple vitamins (vitamin A, C, B6, D, E, folic acid, B-complex vitamins) and other nutrients through supplements (selenium, iron, zinc, calcium, β-carotene, fish oil, iodine, copper, brewer's yeast, magnesium), including brand name and manufacturer of multivitamins, as well as length, frequency, and dose of intake. Copper intake from dietary supplements was calculated based on information collected from the vitamin survey (22).

We characterized midlife dietary copper intake by averaging estimated copper intake from food at visits 1 and 3. We characterized midlife copper intake from supplements based on vitamin survey data at visit 3. We calculated total copper as the sum of copper intake from foods and from supplements.

Cognitive assessments

We considered performance on 3 cognitive tests administered at visits 4 (1996–1998), 5 (2011–2013), and 6 (2016–2017): the Digit Symbol Substitution Test (DSST), the Delayed Word Recall Test (DWRT), and the Word Fluency Test (WFT). The DSST is a test of executive function and psychomotor speed. Participants are asked to relate numbers to symbols using a key within 90 seconds, with a maximum possible score of 93. The score is based on the number of correct symbol-number matches (23). The DWRT is a test of immediate verbal memory, which requires participants to learn a 10-word list and recall as many words as possible after a 5-minute delay (24). The DWRT is scored based on the total number of words that are correctly recalled. The WFT is a test of language and executive function, which scores the participants based on the total number of correctly generated words beginning with 3 letters ("F", "A", "S") in 1 minute for each letter (25). Then z scores

were calculated using the means and standard deviations of individual cognitive tests at baseline, and global z scores were derived from means and standard deviations of the individual z scores, yielding a mean of 0 and a standard deviation of 1.

Adjudication of dementia

Dementia status was determined by computer algorithm using information from cognitive tests and other screening tools, and then confirmed by expert review. When visit-based dementia adjudication was not available, dementia ascertainment was based on the cohort's dementia surveillance efforts (Web Appendix 1, available at https://doi.org/10.1093/aje/kwac040). As such, dementia adjudication was available among those participants who did not attend ARIC visits 5 or 6. Date of onset for dementia was determined to be the earliest date associated with information indicating dementia.

Other covariates

All covariates are based on data collected via self-report or direct measurement at the ARIC cohort examinations. Age at visit 4, sex, race-center, education, smoking status at visit 4, and alcohol consumption status at visit 4 were all collected using standardized, interviewer-administered questionnaires. Body mass index (visit 4) was calculated from measurements of weight to the nearest pound (this was converted to kilograms) and standing height to the nearest centimeter. Height was measured using a wall-mounted ruler with participants not wearing shoes, and weight was measured with a scale zeroed daily and calibrated quarterly. Dietary intake of zinc and iron (which are associated with tau and β-amyloid in the brain) from food, saturated fat, and total intake of energy were calculated from FFQ responses at visit 1 and visit 3, and averaged. We also created a dietary score according to the Dietary Approaches to Stop Hypertension (DASH) diet, based on the average of food intake frequencies collected in the visits 1 and 3 FFQ (26). Participants were awarded 1 to 5 points according to the quintile of intake for each food category. For total fruit, vegetables without potatoes, whole grains, low-fat dairy products, nuts, seeds, and legumes, higher points were given for higher consumption, while lower points were given for higher consumption of red and processed meat, sugar-sweetened beverages, and sodium. The dietary score ranged from 8 to 40 points, with higher scores indicating better adherence to the DASH diet.

Statistical analysis

We estimated the association between dietary copper (mg/day, from food, supplements, total) and incident dementia using survival analysis with parametric models using a Weibull distribution, a framework that works well for aging research, because the incidence rate of dementia increases exponentially with time among older adults (27). The models were adjusted for age, sex, race-center, apolipoprotein E ε4 allele, education, body mass index, smoking, alcohol consumption, total calorie intake, saturated fat intake, zinc intake, iron intake, dietary patterns, and their interactions with time spline terms. Participants with diagnosed dementia at study baseline (visit 4) were excluded from analysis. Potential interactions between dietary copper (grams/day) and high saturated fat intake (defined as the upper 25th percentile) were tested using multiplicative interaction terms. All missing covariates were imputed using multiple imputation chained equations (MICE) models, as described in the Web Appendix 2. We used a burn-in period of 50 iterations, and report final estimates based on combination of 5 imputations, using Rubin's rules (28).

While surveillance allows ascertainment of dementia status regardless of attendance at study visits, cognitive data were available only for those who attended the study visits. To conduct parallel analyses on the associations of dietary copper intake with 20-year cognitive decline, we used MICE to impute the missing information in covariates and cognitive z scores for those who did not attend visit 5 or visit 6, combining previously developed approaches for imputing cognitive data using MICE from visit 2 to visit 5 (12, 29), and from visit 5 to visit 6 (30). To allow analyses of domain-specific cognitive change, we imputed missing DWRT, DSST, and WFT scores directly; missing global z scores were calculated from the imputed DWRT, DSST, and WFT scores. For participants who died during follow-up, final scores were imputed at the date of 6 months prior to death. Among those who were alive but missing information at each visit, we imputed scores at the median date of the study visit. We used a burn-in of 50 iterations, and we report results of regression models based on averaging estimates from 5 of the imputation sets using Rubin's rules. Additional details of the imputation methods are available in Web Table 1. Results of validation and quality control efforts are provided in Web Figures 1–3.

In the imputed data, we estimated the association of dietary copper with 20-year change in cognitive function using linear mixed models. We modeled time using linear splines with a knot at the time of 15 years, which is approximately the time between visits 4 and 5. Models were adjusted for all covariates mentioned above and their interaction terms with time splines. We specified an independence covariance structure (within-subject between parameters) with a random effect for intercept and random effects for each piece of the time spline. A priori, we also examined the potential interaction between dietary copper and high saturated fat intake with cognitive change using multiplicative interaction terms and effect estimates by level of saturated fat intake (above vs. below the 75th percentile). For sensitivity analysis, we conducted complete-case analyses, analyses where only covariates were imputed, and analyses where scores were imputed only for participants who were alive at a given study visit. In addition, we examined the associations of dietary copper and 20-year change in cognitive function in the fully imputed data set without adjustment for dietary components (i.e., dietary score, dietary iron, and dietary zinc).

Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina), and STATA, version 15.1 (StataCorp LLC, College Station, Texas).

RESULTS

Among all 10,269 participants who met the inclusion criteria, the mean age of sample participants was 62.9 (standard deviation, 5.7) years, 43.9% were male, and 18.6% were Black. Of these, 19 (0.2%) had prevalent dementia at visit 4, and were excluded from analyses of incident dementia. The average amount of total copper intake from food and supplements was 1.25 mg/day.

The baseline characteristics of the eligible sample according to amount of copper intake from food and copper intake from supplements are shown in Table 1. Compared with those who were in the lower quartile of copper intake from food adjusted for total caloric intake, participants with a higher proportion of copper intake from food were more likely to be female, Black, college-educated, never smokers, and never drinkers. Those with higher copper intake through food also had, on average, higher diet scores (i.e., greater adherence to the Dietary Approaches to Stop Hypertension (DASH) diet) and lower saturated fat intake, total energy intake, and dietary zinc intake. Compared with those who did not take copper from supplements, those who took copper from supplements (14.7%) were also more likely to be female and college-educated, but less likely to be Black or never drinkers. Those with copper intake through supplements also had lower total energy intake and greater adherence to the DASH diet. The was no correlation between the amount of copper intake from food and that from supplements ($r = 0.01$, $P = 0.61$).

A total of 1,862 incident cases of dementia occurred during follow-up. Web Table 2 shows the number and proportion of incident cases according to total dietary copper intake and saturated fat intake. The crude cumulative incidence of dementia increased with higher total dietary copper intake among participants with high intake of saturated fat (P for linear trend = 0.02). In fully adjusting models, higher intake of total dietary copper intake and dietary copper from food were associated with higher incident dementia only among those with a high intake of saturated fat (hazard ratio = 1.49, 95% confidence interval (CI): 1.04, 1.95) (Table 2). Intake of copper from supplements was not associated with incident dementia either overall or among those with high intake of saturated fat.

The average imputed cognition z scores among all participants were much lower compared with the average complete-cases cognition z scores, and slightly lower compared with average imputed cognition z scores among those known to be alive at each study visit (Web Table 3). Higher total copper intake was associated with greater 20-year decline in WFT overall ($\beta = -0.13$ (95% CI: -0.24, -0.02) excess change in z score per 1-mg increase in daily total copper intake), among those with a high saturated fat intake ($\beta = -0.15$ (95% CI: -0.28, -0.02) excess change in z score per 1-mg higher daily intake in total copper) and among those with non-high saturated fat intake ($\beta = -0.13$ (95% CI: -0.24, -0.01) excess change in z score per 1-mg higher daily intake in total copper). In addition, copper intake from food was associated with greater 20-year decline in WFT overall ($\beta = -0.12$ (95% CI: -0.23, -0.02) excess change in z score per 1-mg higher daily intake in copper from food) and among those with non-high saturated fat intake ($\beta = -0.13$ (95% CI: -0.24, -0.01) excess change in z score per 1-mg higher daily intake in copper from food), and it was marginally associated among those with high saturated fat intake ($\beta = -0.11$ (95% CI: -0.24, 0.02) excess change in z -score per 1-mg higher daily intake in copper from food). Copper intake from supplements was associated with greater 20-year decline in global cognition overall ($\beta = -0.03$ (95% CI: -0.06, -0.0003) excess change in z score per 1-mg higher daily intake in copper from supplements), as well as with 20-year decline in DSST overall ($\beta = -0.06$ (95% CI: -0.10, -0.02) excess change in z score per 1-mg higher daily intake in copper from supplements) and among those with non-high intake of saturated fat ($\beta = -0.06$ (95% CI: -0.10, -0.02) excess change in z score per 1-mg higher daily intake in copper from supplements) (Table 3). The associations between total dietary copper intake and 20-year decline in WFT (overall, and among both high and non-high saturated fat intake groups) and the associations between copper intake from food and 20-year decline in WFT (overall and among non-high saturated fat intake participants) were also statistically significant across all sensitivity analyses (Web Table 4–7).

DISCUSSION

In this large community-based cohort, a 1-mg/day higher intake of total dietary copper during midlife was associated with about 50% higher risk of incident dementia among persons who consumed a diet high in saturated fat, as well as greater decline in verbal fluency over the course of 20 years overall, and within both high and non-high saturated-fat intake groups.

An association between dietary copper intake and cognitive outcomes, particularly in the presence of high saturated fat, is biologically plausible. Copper may oxidize some fat molecules into derivatives, which can be toxic to neurons (31). Copper may also interact with homocysteine to oxidize cholesterol, which then damages the neuron (32). In a rabbit model of Alzheimer disease fed with high cholesterol diet, adding copper to the rabbit's drinking water exacerbated the impact of high-cholesterol diet on neurodegenerative change (i.e., retarding the ability of rabbits to learn a difficult trace conditioning task) (15). In another rabbit model, dietary cholesterol–induced accumulation of β-amyloid, an important biomarker related to Alzheimer disease, increased when the rabbit was fed with distilled water supplemented with 0.12 ppm copper ion, compared with when the rabbit was fed with unaltered distilled water (16). In a mouse model of Alzheimer disease, amyloid accumulation and learning impairment were found among mice fed with 0.1 mg/L copper in drinking water and 2% cholesterol in the food (17).

A few previous studies have examined associations between dietary copper and cognitive outcomes. In data from the Chicago Health and Aging Project, which examined 3,718 participants aged ≥65 years, being in the top quintile of total dietary intake of copper was significantly associated with accelerated cognitive decline (defined as the change of average score of East Boston Tests of Immediate Memory

Table 1. Baseline Characteristics of Participants, Atherosclerosis Risk in Communities Study (*n* = 10,269), United States, 1996–1998

Characteristic	Overall (*n* = 10,269)		Copper From Food								Copper From Supplements			
			Quartile 1: Mean = 0.61 μg/kcal (*n* = 2,568)		Quartile 2: Mean = 0.73 μg/kcal (*n* = 2,567)		Quartile 3: Mean = 0.82 μg/kcal (*n* = 2,566)		Quartile 4: Mean = 0.98 μg/kcal (*n* = 2,568)		Yes (*n* = 1,510)		No (*n* = 8,759)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years[a]	62.9 (5.7)		62.9 (5.7)		62.9 (5.6)		63.0 (5.6)		62.8 (5.8)		63.0 (5.7)		62.9 (5.7)	
Female sex	5,765	56.1	1,006	39.2	1,376	53.6	1,626	63.4	1,757	68.4	959	63.5	4,806	54.9
Black race/ethnicity	1,907	18.6	413	16.1	418	16.3	440	17.2	636	24.8	259	17.2	1,648	18.8
Study center[b]														
Forsyth	2,629	25.6	507	19.7	615	24.0	712	27.8	795	31.0	349	23.1	2,280	26.0
Jackson	1,706	16.6	378	14.7	366	14.3	387	15.1	575	22.4	240	15.9	1,466	16.7
Minneapolis	3,054	29.7	1,032	40.2	841	32.8	701	27.3	480	18.7	492	32.6	2,562	29.3
Washington	2,880	28.1	651	25.4	745	29.0	766	29.9	718	28.0	429	28.4	2,451	28.0
Education														
Below high school	1,774	17.3	473	18.4	427	16.6	432	16.8	442	17.2	187	12.4	1,587	18.1
High school	4,398	42.8	1,136	44.2	1,145	44.6	1,086	42.3	1,031	40.2	624	41.3	3,774	43.1
Some college or higher	4,097	39.9	959	37.3	995	38.8	1,048	40.8	1,095	42.6	699	46.3	3,398	38.8
Apolipoprotein E ε4 allele	2,837	29.8	690	28.9	676	28.4	713	30.0	758	31.7	423	30.2	2,414	29.7
Body mass index[a,c]	28.7 (5.5)		28.5 (5.2)		28.6 (5.4)		28.8 (5.6)		28.9 (5.8)		28.3 (5.4)		28.8 (5.5)	
Smoking														
Never	4,289	41.8	893	34.8	1,074	41.9	1,142	44.6	1,180	46.0	648	42.9	3,641	41.6
Former	4,518	44.1	1,244	48.5	1,134	44.2	1,100	43.0	1,040	40.6	652	43.2	3,886	44.2
Current	1,450	14.1	430	16.8	357	13.9	318	12.4	345	13.5	209	13.9	1,241	14.2
Alcohol consumption														
Never	2,045	19.9	392	15.3	461	18.0	554	21.6	638	24.9	264	17.5	1,781	20.4
Former	2,998	29.2	680	26.5	752	29.3	732	28.6	834	32.5	423	28.0	2,575	29.4
Current	5,216	50.8	1,495	58.2	1,352	52.7	1,276	49.8	1,093	42.6	822	54.5	4,394	50.2
Saturated fat, g/day[a]	21.1 (8.8)		25.6 (9.7)		22.8 (8.4)		19.6 (7.4)		16.4 (6.7)		20.2 (8.6)		21.2 (8.8)	
Iron, g/day[a]	11.4 (4.2)		11.1 (3.9)		11.6 (4.2)		11.6 (4.4)		11.3 (4.5)		11.4 (4.3)		11.4 (4.2)	
Zinc, g/day[a]	10.7 (3.8)		11.3 (4.0)		11.2 (3.9)		10.5 (3.6)		9.7 (3.4)		10.6 (3.8)		10.7 (3.8)	
DASH diet score[a]	24.4 (4.8)		21.9 (4.3)		24.0 (4.5)		25.4 (4.6)		26.3 (4.8)		25.5 (4.7)		24.2 (4.8)	

Table continues

Table 1. Continued

Characteristic	Overall (*n* = 10,269)		Copper From Food								Copper From Supplements			
			Quartile 1: Mean = 0.61 μg/kcal (*n* = 2,568)		Quartile 2: Mean = 0.73 μg/kcal (*n* = 2,567)		Quartile 3: Mean = 0.82 μg/kcal (*n* = 2,566)		Quartile 4: Mean = 0.98 μg/kcal (*n* = 2,568)		Yes (*n* = 1,510)		No (*n* = 8,759)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Dietary source of copper, times/week[a]														
Fish	1.9 (1.7)		1.4 (1.4)		1.7 (1.5)		2.0 (1.8)		2.2 (1.8)		2.1 (1.8)		1.8 (1.6)	
Nuts	0.9 (1.5)		0.6 (0.9)		0.9 (1.2)		0.9 (1.3)		1.3 (2.3)		1.0 (1.6)		0.9 (1.5)	
Chocolate	1.6 (2.4)		1.9 (2.7)		1.9 (2.5)		1.5 (2.2)		1.1 (1.8)		1.6 (2.5)		1.6 (2.3)	
Whole grain bread	5.7 (5.8)		4.6 (5.2)		5.9 (6.0)		6.4 (5.9)		6.1 (5.8)		6.6 (6.0)		5.6 (5.7)	
Cooked cereals	1.3 (1.7)		1.0 (1.5)		1.2 (1.6)		1.4 (1.7)		1.4 (2.0)		1.3 (1.8)		1.2 (1.7)	
Total energy intake, kcal/day[a]	1614.2 (514.9)		1771.8 (547.9)		1680.0 (499.3)		1574.3 (482.3)		1430.6 (462.7)		1584.7 (500.5)		1619.3 (517.2)	
DSST score[a]	44.1 (13.1)		43.5 (13.0)		44.6 (12.8)		44.8 (13.0)		43.7 (13.6)		45.6 (12.6)		43.9 (13.2)	
DWRT score[a]	6.6 (1.5)		6.5 (1.5)		6.6 (1.5)		6.7 (1.5)		6.6 (1.6)		6.7 (1.5)		6.6 (1.5)	
WFT score[a]	33.8 (12.4)		33.2 (12.4)		34.0 (12.1)		34.1 (12.4)		34.1 (12.6)		35.4 (12.4)		33.6 (12.4)	

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; DSST, Digit Symbol Substitution Test; DWRT, Delayed Word Recall Test; WFT, Word Fluency Test.

[a] Continuous variables are expressed as mean (standard deviation).

[b] Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland.

[c] Body mass index is calculated as weight (kg)/height $(m)^2$.

Table 2. Hazard Ratios[a] for Incident Dementia by 2017 Associated With Dietary Copper Intake (n = 10,250) in the Atherosclerosis Risk in Communities Study, United States

Type of Copper	Overall		With High Saturated Fat Intake		With Non-High Saturated Fat Intake	
	HR	95% CI	HR	95% CI	HR	95% CI
Total copper	1.17	0.89, 1.45	1.50	1.00, 2.00	1.05	0.78, 1.33
Copper from food	1.20	0.92, 1.48	1.49	1.04, 1.95	1.08	0.81, 1.36
Copper from supplements	0.98	0.91, 1.04	1.01	0.85, 1.16	0.97	0.90, 1.05

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Models adjusted for age, sex, race-center, apolipoprotein E ε4 allele, education, body mass index, smoking, alcohol consumption, total calorie intake, saturated fat intake, zinc intake, iron intake, and dietary patterns. P for interaction between copper from food and high saturated fat is 0.03; P for interaction between copper from supplements and high saturated fat is 0.68; and P for interaction between total copper and high saturated fat is 0.03.

and Delayed Recall, the Mini-Mental State Examination, and the Symbol Modalities Test) over 6 years among participants with high intake of saturated and trans fats (18). However, the results differed from our findings, since we did not find an association between dietary copper and change in global cognition among those with high saturated fat intake. The different findings between the 2 studies may be attributed to differences in age at baseline (≥65 years), length of follow-up period (smaller proportion of attrition during 6 years), inclusion of trans fat, and different cognitive tests (with Mini-Mental State Examination) in the Chicago Health and Aging Project study. In a second study, Li et al. (33) found that copper intake in the highest quartile was associated with lower odds of low DSST in a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) 2011–2014. However, compared with longitudinal studies, the cross-sectional analysis may be more likely to suffer from issues of temporality.

The recommended daily value of total copper intake from food and supplements is 0.9 mg/day (34), and the average total intake of copper among adults 20 years and older in the United States (1.4–1.7 mg/day) has exceeded the daily value (35). It is worth noting that our results suggested that the associations of dietary copper and cognitive outcomes depended not only on the amount of copper but also the source of copper. The association of total dietary copper intake with incident dementia and decline in WFT was driven by dietary copper intake from food but not supplements. This may be attributed to the fact that people taking high amounts of copper from food and from supplements showed different baseline characteristics. Also, the different bioavailability of copper from food and supplements may contribute to different associations between dietary copper and cognitive outcomes. Particularly, copper in supplements is likely to have different forms, to be combined with different minerals, and to be displaced when interacting with other minerals (36). Future studies should further explore how dietary copper from different sources affects cognitive outcomes.

Our study had several strengths. Use of multiple imputation chained equations enabled us to conduct parallel analyses for dementia and cognitive change, addressing the potential issues of selection bias due to loss to follow-up. Our study also benefited from a large sample of participants with assessment of diet in middle-age and a long period of follow-up, enabling us to observe the association between dietary copper and cognitive change from midlife to late life. In addition, since the assessments of dietary intake were conducted prior to that of cognitive assessment, we were able to establish temporality between our exposure and outcome.

However, our study also suffered from limitations. First, the content of copper in food can be affected by some environmental factors, such as soil copper concentration, use of copper compound–containing bactericides or fungicides on crops, and local copper emissions from industry (1). These variations cannot be reflected in the FFQ. The associations of dietary copper and cognition may also be affected by copper from sources other than foods and supplements, including copper intake from drinking water, which we were not able to measure. Also, due to the complexity of cognitive function, 3 cognitive tests may not be sufficient to evaluate global cognition and cannot provide insight into associations with performance on other cognitive domains (e.g., spatial reasoning, attention) or processing speed. Similarly, while prior studies have shown associations between risk factors and these tests, they may not be sensitive enough to identify subtle accelerations of cognitive change due to dietary copper intake given the overall cognitive status of our cohort.

In conclusion, higher intake of dietary copper intake is associated with higher risk of incident dementia, particularly in those with high saturated fat intake. The associations may be driven by the associations between dietary copper intake and decline in language. Our study suggests that dietary copper intake may be a novel risk factor for incident dementia; however, given differences with prior epidemiologic findings, further work is needed to confirm these associations in other contexts.

Table 3. Associations Between Dietary Copper and 20-Year Cognitive Decline, With Imputation of Missing Covariates and Outcomes for All Eligible Participants (n = 10,269) in the Atherosclerosis Risk in Communities Study, United States, 1996–1998 to 2016–2017[a]

Copper and Saturated Fat Intake	No. of Years					
	1–15		16–20		1–20	
	β	95% CI	β	95% CI	β	95% CI
			Global z Score			
Overall						
Total copper	−0.002	−0.10, 0.09	−0.04	−0.21, 0.12	−0.05	−0.20, 0.10
Copper from food	−0.02	−0.11, 0.08	0.003	−0.16, 0.17	−0.01	−0.16, 0.13
Copper from supplements	0.02	−0.01, 0.04	−0.05	−0.08, −0.02	−0.03	−0.06, −0.0003
High saturated fat						
Total copper	0.02	−0.10, 0.15	−0.03	−0.22, 0.17	−0.004	−0.17, 0.17
Copper from food	0.02	−0.10, 0.14	0.02	−0.16, 0.20	0.05	−0.11, 0.20
Copper from supplements	0.001	−0.05, 0.05	−0.05	−0.13, 0.03	−0.05	−0.13, 0.03
Non-high saturated fat						
Total copper	−0.02	−0.12, 0.08	−0.06	−0.22, 0.11	−0.07	−0.23, 0.09
Copper from food	−0.04	−0.13, 0.06	−0.01	−0.17, 0.16	−0.04	−0.20, 0.12
Copper from supplements	0.02	−0.01, 0.05	−0.05	−0.08, −0.01	−0.03	−0.06, 0.005
			Digit Symbol Substitution Test			
Overall						
Total copper	0.03	−0.05, 0.11	−0.07	−0.17, 0.02	−0.04	−0.15, 0.06
Copper from food	0.04	−0.05, 0.12	−0.02	−0.11, 0.07	0.01	−0.09, 0.12
Copper from supplements	−0.01	−0.03, 0.02	−0.05	−0.08, −0.02	−0.06	−0.10, −0.02
High saturated fat						
Total copper	0.07	−0.03, 0.18	−0.06	−0.19, 0.06	0.01	−0.13, 0.15
Copper from food	0.07	−0.03, 0.18	−0.02	−0.13, 0.09	0.05	−0.08, 0.18
Copper from supplements	−0.001	−0.05, 0.05	−0.04	−0.10, 0.03	−0.04	−0.10, 0.02
Non-high saturated fat						
Total copper	0.01	−0.08, 0.10	−0.08	−0.18, 0.02	−0.07	−0.17, 0.03
Copper from food	0.02	−0.07, 0.11	−0.02	−0.12, 0.07	−0.01	−0.11, 0.10
Copper from supplements	−0.01	−0.04, 0.02	−0.05	−0.09, −0.02	−0.06	−0.10, −0.02
			Delayed Word Recall Test			
Overall						
Total copper	0.03	−0.11, 0.17	0.04	−0.21, 0.29	0.08	−0.14, 0.29
Copper from food	−0.003	−0.14, 0.14	0.09	−0.16, 0.34	0.09	−0.12, 0.29
Copper from supplements	0.04	−0.01, 0.08	−0.05	−0.09, −0.003	−0.01	−0.06, 0.04
High saturated fat						
Total copper	0.05	−0.14, 0.24	0.11	−0.21, 0.42	0.16	−0.10, 0.41
Copper from food	0.04	−0.15, 0.23	0.15	−0.14, 0.43	0.19	−0.04, 0.41
Copper from supplements	0.01	−0.08, 0.10	−0.04	−0.16, 0.08	−0.03	−0.15, 0.09
Non-high saturated fat						
Total copper	0.02	−0.13, 0.17	0.01	−0.25, 0.26	0.03	−0.20, 0.26
Copper from food	−0.02	−0.17, 0.12	0.06	−0.20, 0.32	0.04	−0.18, 0.26
Copper from supplements	0.04	−0.01, 0.10	−0.05	−0.10, 0.0004	−0.01	−0.06, 0.04

Table continues

Table 3. Continued

Copper and Saturated Fat Intake	No. of Years					
	1–15		16–20		1–20	
	β	95% CI	β	95% CI	β	95% CI
	Word Fluency Test					
Overall						
Total copper	−0.07	−0.15, 0.02	−0.07	−0.17, 0.04	−0.13	−0.24, −0.02
Copper from food	−0.07	−0.15, 0.02	−0.06	−0.16, 0.05	−0.12	−0.23, −0.02
Copper from supplements	0.003	−0.02, 0.03	−0.01	−0.04, 0.02	−0.01	−0.04, 0.02
High saturated fat						
Total copper	−0.07	−0.18, 0.05	−0.08	−0.23, 0.06	−0.15	−0.28, −0.02
Copper from food	−0.07	−0.18, 0.05	−0.05	−0.19, 0.08	−0.11	−0.24, 0.02
Copper from supplements	−0.01	−0.07, 0.05	−0.03	−0.09, 0.03	−0.04	−0.10, 0.02
Non-high saturated fat						
Total copper	−0.07	−0.16, 0.03	−0.06	−0.17, 0.05	−0.13	−0.24, −0.01
Copper from food	−0.07	−0.17, 0.02	−0.05	−0.17, 0.06	−0.13	−0.24, −0.01
Copper from supplements	0.01	−0.02, 0.03	−0.004	−0.04, 0.03	0.002	−0.03, 0.04

Abbreviation: CI, confidence interval.

[a] Mixed models adjusted for age, sex, race-center, apolipoprotein E ε4 allele, education, body mass index, smoking, alcohol consumption, total calorie intake, saturated fat intake, zinc intake, iron intake, dietary patterns, and their interactions with time spline terms.

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Author affiliations: Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, United States (Jingkai Wei); Department of Epidemiology, Milken Institute School of Public Health, George Washington University, Washington, DC, United States (Jingkai Wei, Kan Z. Gianattasio, Erin E. Bennett, Melinda C. Power); Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (James D. Stewart, Eric A. Whitsel); Department of Epidemiology and Biostatistics, School of Public Health, Texas A&M University, College Station, Texas, United States (Xiaohui Xu); Texas A&M Transportation Institute, Texas A&M University System, College Station, Texas, United States (Eun Sug Park); Department of Statistics and Operations Research, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (Richard L. Smith); Zachry Department of Civil and Environmental Engineering, Texas A&M University, College Station, Texas, United States (Qi Ying); and Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (Eric A. Whitsel).

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REFERENCES

1. Bost M, Houdart S, Oberli M, et al. Dietary copper and human health: current evidence and unresolved issues. *J Trace Elem Med Biol.* 2016;35:107–115.
2. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. *Lancet Neurol.* 2015; 14(1):103–113.
3. Mathys ZK, White AR. Copper and Alzheimer's disease. *Adv Neurobiol.* 2017;18:199–216.
4. Ma Q, Li Y, Du J, et al. Copper binding properties of a tau peptide associated with Alzheimer's disease studied by CD, NMR, and MALDI-TOF MS. *Peptides.* 2006;27(4): 841–849.
5. Ma QF, Li YM, Du JT, et al. Binding of copper (II) ion to an Alzheimer's tau peptide as revealed by MALDI-TOF MS, CD, and NMR. *Biopolymers.* 2005;79(2):74–85.
6. Xu H, Finkelstein DI, Adlard PA. Interactions of metals and apolipoprotein E in Alzheimer's disease. *Front Aging Neurosci.* 2014;6:121.
7. Agarwal R, Kushwaha SS, Tripathi CB, et al. Serum copper in Alzheimer's disease and vascular dementia. *Indian J Clin Biochem.* 2008;23(4):369–374.
8. Park JH, Lee DW, Park KS. Elevated serum copper and ceruloplasmin levels in Alzheimer's disease. *Asia Pac Psychiatry.* 2014;6(1):38–45.
9. Squitti R, Bressi F, Pasqualetti P, et al. Longitudinal prognostic value of serum "free" copper in patients with Alzheimer disease. *Neurology.* 2009;72(1):50–55.
10. Salustri C, Barbati G, Ghidoni R, et al. Is cognitive function linked to serum free copper levels? A cohort study in a normal population. *Clin Neurophysiol.* 2010;121(4): 502–507.
11. Ma C, Yin Z, Zhu P, et al. Blood cholesterol in late-life and cognitive decline: a longitudinal study of the Chinese elderly. *Mol Neurodegener.* 2017;12(1):24.
12. Power MC, Rawlings A, Sharrett AR, et al. Association of midlife lipids with 20-year cognitive change: a cohort study. *Alzheimers Dement.* 2018;14(2):167–177.
13. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. *J Alzheimers Dis.* 2017;56(1):215–228.
14. Mielke MM, Xue Q-L, Zhou J, et al. Baseline serum cholesterol is selectively associated with motor speed and not rates of cognitive decline: the Women's Health and Aging Study II. *J Gerontol A Biol Sci Med Sci.* 2008;63(6):619–624.
15. Sparks DL, Schreurs BG. Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. *Proc Natl Acad Sci U S A.* 2003;100(19):11065–11069.
16. Larry SD. Cholesterol, copper, and accumulation of thioflavine S-reactive Alzheimer's-like amyloid beta in rabbit brain. *J Mol Neurosci.* 2004;24(1):097–104.
17. Yao D, Jing T, Niu L, et al. Amyloidogenesis induced by diet cholesterol and copper in a model mouse for Alzheimer's disease and protection effects of zinc and fluvastatin. *Brain Res Bull.* 2018;143:1–8.
18. Morris MC, Evans DA, Tangney CC, et al. Dietary copper and high saturated and trans fat intakes associated with cognitive decline. *Arch Neurol.* 2006;63(8):1085–1088.
19. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. The ARIC investigators. *Am J Epidemiol.* 1989;129(4):687–702.
20. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122(1):51–65.
21. Yuan C, Spiegelman D, Rimm EB, et al. Validity of a dietary questionnaire assessed by comparison with multiple weighed dietary records or 24-hour recalls. *Am J Epidemiol.* 2017; 185(7):570–584.
22. Peacock JM, Folsom AR, Knopman DS, et al. Dietary antioxidant intake and cognitive performance in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) study investigators. *Public Health Nutr.* 2000;3(3):337–343.
23. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale, Revised*. New York, NY: The Psychological Corporation; 1981.
24. Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Arch Neurol.* 1989;46(2):141–145.
25. Lezak M, Howieson D, Loring D. *Neuropsychological Assessment*. 4th ed. New York, NY: Oxford University Press, Inc; 2004.
26. Fung TT, Chiuve SE, McCullough ML, et al. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med.* 2008;168(7):713–720.
27. Ganguli M, Lee C-W, Snitz BE, et al. Rates and risk factors for progression to incident dementia vary by age in a population cohort. *Neurology.* 2015;84(1):72–80.
28. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons; 2004.
29. Rawlings AM, Sang Y, Sharrett AR, et al. Multiple imputation of cognitive performance as a repeatedly measured outcome. *Eur J Epidemiol.* 2017;32(1):55–66.
30. Wu A, Sharrett AR, Deal Jennifer A, et al. Abstract P018: smoking and cognitive decline at older age: using surveillance and imputation to deal with differential mortality. *Circulation.* 2019;139(suppl 1):AP018.
31. Brewer GJ. Alzheimer's disease causation by copper toxicity and treatment with zinc. *Front Aging Neurosci.* 2014;6:92.
32. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways. *J Neurochem.* 2001;76(5):1509–1520.
33. Li S, Sun W, Zhang D. Association of Zinc, iron, copper, and selenium intakes with low cognitive performance in older adults: a cross-sectional Study from National Health and Nutrition Examination Survey (NHANES). *J Alzheimers Dis.* 2019;72(4):1145–1157.
34. Food and Drug Administration. Final rule. food labeling: revision of the nutrition and supplement facts labels. Federal Register 81, no. 103 (May 27, 2016). 33741–33999.
35. Office of Dietary Supplements. Copper: fact sheet for health professionals. National Institutes of Health; 2021. https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/. Accessed April 6, 2022.
36. Wapnir RA. Copper absorption and bioavailability. *Am J Clin Nutr.* 1998;67(5):1054s–1060s.