Dietary Copper and High Saturated and trans Fat Intakes Associated With Cognitive Decline

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Background: Evidence from prospective epidemiologic studies and animal models suggests that intakes of dietary fats and copper may be associated with neurodegenerative diseases.

Objective: To examine whether high dietary copper intake is associated with increased cognitive decline among persons who also consume a diet high in saturated and trans fats.

Design: Community-based prospective study.

Setting: Chicago, Ill.

Patients: Chicago residents 65 years and older.

Main Outcome Measures: Cognitive function was assessed using 4 cognitive tests administered during in-home interviews at 3-year intervals for 6 years. Dietary assessment was performed with a food frequency questionnaire. Dietary intakes of copper and fats were related to change in global cognitive score (the mean of the 4 tests) among 3718 participants.

Results: Among persons whose diets were high in saturated and trans fats, higher copper intake was associated with a faster rate of cognitive decline. In multiple-adjusted mixed models, the difference in rates for persons in the highest (median, 2.75 mg/d) vs lowest (median, 0.88 mg/d) quintiles of total copper intake was −6.14 standardized units per year (P < .001) or the equivalent of 19 more years of age. There was also a marginally statistically significant association (P = .07) with the highest quintile of food intake of copper (median, 1.51 mg/d) and a strong dose-response association with higher copper dose in vitamin supplements. Copper intake was not associated with cognitive change among persons whose diets were not high in these fats.

Conclusion: These data suggest that high dietary intake of copper in conjunction with a diet high in saturated and trans fats may be associated with accelerated cognitive decline.

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Evidence from prospective epidemiologic studies1,2 and animal models3 suggests that dietary fat intake may be associated with cognitive decline. In previous studies, we observed an increased risk of incident Alzheimer disease4 and cognitive decline5 among persons whose diets were high in saturated and trans fats and low in unhydrogenated unsaturated fats. In humans, this type of fat composition results in an unfavorable blood cholesterol profile.4 A recent animal study6 found that neurodegenerative changes caused by a hypercholesterolemic diet may be exacerbated by consumption of trace amounts of copper in drinking water. Copper, zinc, and iron are essential for normal brain functioning and development. However, dyshomeostasis of these metals is thought to play a central role in the formation and neurotoxicity of amyloid-β (Aβ) and neurofibrillary tangles.5-8 In this investigation, we tested the hypothesis that persons who have high copper consumption in conjunction with a diet high in saturated and trans fats are at increased risk of cognitive decline.

Methods

A total of 6138 community residents (overall response, 78.9%) 65 years and older, who were all participants in the ongoing Chicago Health and Aging Project (CHAP),9 participated in home interviews that included cognitive testing. Participants completed a food frequency questionnaire (FFQ) a median of 1.2 years after baseline. Reassessments of cognitive function were conducted at 3-year and 6-year follow-up interviews. The institutional review
Cognitive scores declined on average by 4.2 standardized units per year (SU/yr). Persons with high copper intakes were more likely to have healthy lifestyle behaviors and higher cognitive ability (Table 1).

Overall, dietary intakes of copper, zinc, and iron were not associated with cognitive decline after adjustment for fat was in the upper 60%. These a priori, arbitrarily defined levels were guided by our previous studies of fat intake and risk of Alzheimer disease and cognitive decline. In a validity study of CHAP participants, Pearson correlations between total intake levels on the FFQ and multiple 24-hour dietary recalls were 0.46 for copper, 0.50 for zinc, and 0.43 for iron.

Interviewers administered 4 cognitive tests at each interview: the East Boston Tests of Immediate Memory and Delayed Recall, the Mini-Mental State Examination, and the Symbol Digit Modalities Test. We computed z scores for each test using the means and standard deviations from the baseline study population and averaged these into a single global measure.

A total of 4390 participants (88% of the surviving participants) completed at least 2 cognitive assessments and an FFQ, of whom we eliminated 217 who had a potentially invalid FFQ and 460 who completed the FFQ more than 2.5 years after baseline. Therefore, 3718 persons were analyzed, with a median follow-up of 3.5 years.

The cognitive activity score was derived from a composite measure of frequency of participation in 7 cognitive activities. Physical activity was based on participation in 9 activities (hours per week). Heart disease was determined by history of myocardial infarction or use of digitalis. Hypertension was determined by self-report or a measured systolic blood pressure of 160 mm Hg or higher or diastolic blood pressure of 95 mm Hg or higher. Stroke history was determined through self-report. Diabetes mellitus was determined either by self-report or use of antidiabetic medication.

We used mixed-effects models with SAS statistical software (SAS Institute Inc, Cary, NC) to estimate risk factor associations with cognitive change. The model accounts for correlations among the cognitive scores within persons and controls for overall level of cognitive ability. Before the analyses, we determined the best model of the covariates by considering non-linear associations and interactions among covariates. Coefficients were multiplied by a factor of 100.

Table 1. Age-Standardized Baseline Characteristics by Total Intake Level of Copper Among 3718 Participants in the Chicago Health and Aging Project, 1993-2002*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td>No. of participants</td>
<td>729</td>
<td>754</td>
<td>727</td>
<td>782</td>
<td>746</td>
</tr>
<tr>
<td>Range of total copper intake, mg/d</td>
<td>0.5-1.0</td>
<td>1.0-1.1</td>
<td>1.1-1.3</td>
<td>1.3-1.6</td>
<td>1.6-8.3</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>74.5</td>
<td>74.8</td>
<td>74.3</td>
<td>74.0</td>
<td>74.0</td>
</tr>
<tr>
<td>Female, %</td>
<td>65.8</td>
<td>61.6</td>
<td>57.9</td>
<td>57.7</td>
<td>67.1</td>
</tr>
<tr>
<td>African American, %</td>
<td>69.5</td>
<td>62.6</td>
<td>59.0</td>
<td>62.2</td>
<td>48.5</td>
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<tr>
<td>Global cognitive score, mean</td>
<td>5.5</td>
<td>15.3</td>
<td>19.1</td>
<td>18.7</td>
<td>34.1</td>
</tr>
<tr>
<td>MMSE score, mean</td>
<td>26.0</td>
<td>26.4</td>
<td>26.5</td>
<td>26.5</td>
<td>27.2</td>
</tr>
<tr>
<td>Education, mean, y</td>
<td>11.6</td>
<td>12.0</td>
<td>12.3</td>
<td>12.3</td>
<td>12.9</td>
</tr>
<tr>
<td>Cognitive activities score, mean</td>
<td>3.0</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Physical activities, mean, h/wk</td>
<td>3.0</td>
<td>3.5</td>
<td>3.6</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Alcohol consumption, mean, g/d</td>
<td>5.7</td>
<td>4.4</td>
<td>3.9</td>
<td>3.0</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination.
*All variables (except age) are adjusted for age in 5-year age categories using the total Chicago Health and Aging Project population as the reference.

Table 2. Age- and Multiple-Adjusted Differences in the Estimated Annual Rate of Change in Cognitive Score During 6 Years by Intake Level of Copper, Zinc, and Iron Among 3718 Participants in the Chicago Health and Aging Project, 1993-2002*

<table>
<thead>
<tr>
<th>Model</th>
<th>Copper (SE)</th>
<th>Zinc (SE)</th>
<th>Iron (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Age adjusted†</td>
<td>-.46 (.02)</td>
<td>-.02 (.02)</td>
<td>.02 (.01)</td>
</tr>
<tr>
<td>P value</td>
<td>.05</td>
<td>.36</td>
<td>.17</td>
</tr>
<tr>
<td>Multiple adjusted‡</td>
<td>-.41 (.02)</td>
<td>-.02 (.02)</td>
<td>.02 (.01)</td>
</tr>
<tr>
<td>P value</td>
<td>.16</td>
<td>.28</td>
<td>.11</td>
</tr>
<tr>
<td>Food Age adjusted†</td>
<td>1.46 (.02)</td>
<td>.19 (.09)</td>
<td>.07 (.06)</td>
</tr>
<tr>
<td>P value</td>
<td>.08</td>
<td>.05</td>
<td>.20</td>
</tr>
<tr>
<td>Multiple adjusted‡</td>
<td>.31 (.01)</td>
<td>.15 (.17)</td>
<td>-.03 (.08)</td>
</tr>
<tr>
<td>P value</td>
<td>.68</td>
<td>.37</td>
<td>.67</td>
</tr>
</tbody>
</table>

*The β coefficients were multiplied by 100.
†Age-adjusted models included terms for copper, zinc, and iron (in milligrams per day), age, age squared, time (in years) of observation, and interaction terms between time and each covariate.
‡Multiple-adjusted models included terms from the age-adjusted model plus sex, race, education (in years), cognitive activities, physical activities, alcohol consumption (in grams per day), stroke, heart disease, hypertension, diabetes mellitus, vitamin E in food (in milligrams per day), total vitamin C (in milligrams per day), niacin in food (in milligrams per day), total folate (in micrograms per day), saturated fat (in grams per day), trans fat (in grams per day), and polyunsaturated fat (in grams per day).
The decline was seen with higher copper consumption. Among the 604 persons (16.2%) who consumed a diet high in saturated and trans fats, there was no association in the low-fat group. However, consistent with our hypothesis, among the 604 persons who consumed a diet high in saturated and trans fats, a faster decline was seen with higher copper consumption. There was a 143% increase in the decline rate (a difference of 6.14 SU/y; \( P < .001 \)) among persons in the highest quintile of total copper intake (median, 2.75 mg/d) compared with those in the lowest quintile (median, 0.88 mg/d) in the multiple-adjusted model. No association was seen with copper intake among persons who had low consumption of these fats. A similar, although weaker, association was observed with copper intake from food sources only (Table 3).

We examined copper interaction effects with intakes of saturated fat (highest 20% of intake vs lower 80%) and trans fats (highest 60% vs lower 40%) individually; however, neither interaction was as strong as the combined high-fat variable. The interaction with a high-fat diet was specific to copper intake and was not apparent with intakes of zinc or iron. In addition, no interaction effects were found between copper intake and dietary cholesterol or other types of fat.

In further analyses, we investigated the relationship according to copper dose in vitamin supplements (consumed by 602 persons [17%]), in which nonsupplement users were analyzed with a vitamin dose of 0. Higher copper dose was strongly associated with cognitive decline in the high-fat group (−3.39 SU/y per milligram per day of copper; \( P < .001 \)) in the multiple-adjusted model that was also adjusted for copper intake from food, but there was no association in the low-fat group.

The multiple-adjusted estimates of effect for the copper-fat interaction changed little and remained statistically significant (rate difference for the fifth quintile = −7.25; \( P < .001 \)) in Table 3. However, consistent with our hypothesis, among the 604 persons (16.2%) who consumed a diet high in saturated and trans fats, a faster decline was seen with higher copper consumption (Table 2). There was a 143% increase in the decline rate (a difference of 6.14 SU/y; \( P < .001 \)) among persons in the highest quintile of total copper intake (median, 2.75 mg/d) compared with those in the lowest quintile (median, 0.88 mg/d) in the multiple-adjusted model. No association was seen with copper intake among persons who had low consumption of these fats. A similar, although weaker, association was observed with copper intake from food sources only (Table 3).

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The multiple-adjusted estimates of effect for the copper-fat interaction changed little and remained statistically significant (rate difference for the fifth quintile = −7.25; \( P < .001 \)) when we reanalyzed the data after excluding 1012 persons who reported fair or poor health. The relation-
tive stress in patients with Alzheimer disease and slowed cognitive decline compared with placebo.\textsuperscript{19} In several case-control studies, patients with Alzheimer disease were distinguished by high serum copper levels compared with patients with vascular dementia\textsuperscript{10} or mild cognitive impairment\textsuperscript{20} or with cognitively healthy individuals.\textsuperscript{21}

A limitation of our study is the potential for inaccurate measurement of dietary copper, because the copper content of plant foods depends on the soil and this varies by region. It is unlikely that this limitation can account for the study findings, which were strongest for copper intake from multivitamins. It is also unclear to what extent copper water pipes contribute to the level of intake from tap water. However, the absence of data on copper intake from water and other sources would likely result in random error and thus bias the estimates of effect toward the null.

The observational study design of CHAP limits causal interpretation. In addition, the analyses were an extension of earlier findings of dietary fat associations with cognitive decline, which has the disadvantage of multiple comparisons and greater likelihood of chance findings. Several points argue against chance or confounding as explanations, however, including significance levels of $P < .001$, the extraordinarily large estimate of effect (the equivalent of 19 more years of age) even after adjustment for numerous lifestyle factors, and the fact that the copper-fat interaction was our a priori hypothesis. Furthermore, the associations between high copper intake and both higher education and cognitive activity argue against unrecognized confounding as an explanation.

Organ meats and shellfish are the richest food sources of copper. The more abundant plant sources include nuts, seeds, legumes, whole grains, some fruits, potatoes, and chocolate. The current recommended dietary allowance for copper intake for adults is 0.9 mg/d. However, CHAP did not find that high copper intake alone was related to cognitive decline.

This finding of accelerated cognitive decline among persons whose diets were high in copper and saturated and trans fats must be viewed with caution. The supporting evidence on this topic is limited. The strength of the association and the potential impact on public health warrant further investigation.

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Author Contributions: Study concept and design: Morris, Evans, and Wilson. Acquisition of data: Morris, Evans, Tangney, and Scherr. Analysis and interpretation of data: Morris, Evans, Tangney, Bienias, and Schneider. Drafting of the manuscript: Morris. Critical revision of the manuscript for important intellectual content: Morris, Evans, Bienias, Schneider, Wilson, and Scherr. Statistical analysis: Morris and Bienias. Obtained funding: Morris, Evans, and Wilson. Administrative, technical, and material support: Morris, Evans, Schneider, and Wilson. Study supervision: Evans.

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