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Accessibility
Dietary Fat Intake and Cognitive Decline in Women With Type 2 Diabetes

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OBJECTIVE — Individuals with type 2 diabetes have high risk of late-life cognitive impairment, yet little is known about strategies to modify risk. Targeting insulin resistance and vascular complications—both associated with cognitive decline—may be a productive approach. We investigated whether dietary fat, which modulates glucose and lipid metabolism, might influence cognitive decline in older adults with diabetes.

RESEARCH DESIGN AND METHODS — Beginning in 1995–1999, we evaluated cognitive function in 1,486 Nurses’ Health Study participants, aged ≥70 years, with type 2 diabetes; second evaluations were conducted 2 years later. Dietary fat intake was assessed regularly beginning in 1980; we considered average intake from 1980 (at midlife) through initial cognitive interview and also after diabetes diagnosis. We used multivariate-adjusted linear regression models to obtain mean differences in cognitive decline across tertiles of fat intake.

RESULTS — Higher intakes of saturated and trans fat since midlife, and lower polyunsaturated to saturated fat ratio, were each highly associated with worse cognitive decline in these women. On a global score averaging all six cognitive tests, mean decline among women in the highest trans fat tertile was 0.15 standard units worse than that among women in the lowest tertile (95% CI −0.24 to −0.06, P = 0.002); this mean difference was comparable with the difference we find in women 7 years apart in age. Results were similar when we analyzed diet after diabetes diagnosis.

CONCLUSIONS — These findings suggest that lower intakes of saturated and trans fat and higher intake of polyunsaturated fat relative to saturated fat may reduce cognitive decline in individuals with type 2 diabetes.

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Type 2 diabetes has reached epidemic proportions in most Western countries, including 20 million individuals affected in the U.S. (1). Cardiovascular disease, kidney failure, and neuropathy are known sequelae, but cognitive impairment is increasingly recognized as a further complication at older ages (2). Therefore, identifying strategies to prevent or delay diabetes-related cognitive impairment is a growing public health concern. Dietary fat intake can alter glucose and lipid metabolism (3) and is related to cardiovascular disease risk in individuals with type 2 diabetes (4). Because insulin, cholesterol, and vascular disease all appear to play important roles in brain aging and cognitive impairments (5), dietary fat modification may be a particularly effective strategy for preventing cognitive decline, especially in individuals with diabetes. Thus, we studied nearly 1,500 Nurses’ Health Study participants with type 2 diabetes to evaluate the relation between dietary fat intake and subsequent cognitive decline.

RESEARCH DESIGN AND METHODS — The Nurses’ Health Study began in 1976, when 121,700 registered nurses, aged 30–55 years, completed a mailed questionnaire about their health and lifestyle, including type 2 diabetes. Follow-up questionnaires are mailed every 2 years, and a food-frequency questionnaire was added in 1980. All self-reported diabetes case subjects were sent a supplemental questionnaire to ascertain symptoms, diagnostic tests, and treatment; standard criteria were used to confirm type 2 diabetes. In a validation study, we found that medical record review corroborated 98% of self-reported diabetes cases (6). Furthermore, in a random sample of participants who reported no diagnosis of diabetes, <2% had diagnostic evidence of diabetes in blood tests (7); this suggests that underreporting or underdiagnosis of diabetes is likely minimal in this population of health professionals with good health knowledge and access to health care.

Starting in 1995–1999, Nurses’ Health Study participants aged ≥70 years were selected for a study of cognitive function; the first years were largely pilot interviews, and the vast majority of baseline data were collected in 1998–1999. A telephone interview was conducted in community-dwelling women who were free of stroke; 93% of eligible women participated (n = 19,415) and 7% refused. Follow-up interviews were conducted ~2 years later (mean 1.8 years, range 1.3–4.7), and participation rates were >90% for women who were still alive. Preliminary data are also available from an additional follow-up assessment (mean follow-up 4.2 years). The Institutional Review Board of Brigham and Women’s Hospital (Boston, MA) approved this study. For questionnaire information, return of the questionnaire implied informed consent, and we obtained oral consent for the cognitive study.

Dietary assessment — We used a Willett semiquantitative food frequency questionnaire (8) to assess dietary habits in 1980, 1984, 1986, and ev-
Dietary fat and cognitive decline

On average, women completed five dietary assessments during the analysis period and three assessments after diabetes diagnosis. We observed few meaningful differences in health and lifestyle across tertiles of several major fat types, with intake averaged since midlife (Table 1). However, women with higher intakes of saturated and trans fats were slightly less likely to take vitamin E supplements and had slightly higher preva-
and duration of diabetes (H11021).

Baseline cognition (continuous), time between cognitive interviews (continuous), BMI (continuous), physical activity (continuous), diabetes medication (none, oral hypoglycemic medication only, insulin use), and duration of diabetes (<5, 5–9, 10–14, and ≥15 years). *Fat intake is expressed as a percentage of total energy consumption.

For diet since midlife, we found significantly worse cognitive decline on the global score with increasing intakes of saturated (P trend = 0.002) and trans fat (P trend = 0.002) (Table 2). For example, women in the highest tertile of trans fat intake had a mean decline in the global score that was 0.15 standard units (95% CI −0.24 to −0.06) worse than those in the lowest tertile, after multivariable adjustment for age, education, BMI, physical activity, and measures of diabetes severity. Results were virtually identical with further adjustment for depression, vitamin E supplement use, alcohol intake, smoking status, and history of high blood pressure, high cholesterol, or myocardial infarction (mean difference in decline = 0.16 standard units; 95% CI −0.25 to −0.07, comparing extreme tertiles of trans fat) (data not shown in Table 2). For saturated fat, the mean difference in global decline was −0.12 standard units (95% CI −0.22 to −0.01) comparing top and bottom tertiles. To help interpret these results, we compared these effect estimates to those we found for the relation of age to cognitive decline in our population. We found that a 1-year age increase was associated with a mean global score of 0.06 (95% CI 0.04 to 0.08). We also found that women in the highest tertile of trans fat were somewhat more likely to use vitamin E supplements.

Women in the highest tertile of history of high cholesterol (women with high cholesterol may have initiated dietary changes). In addition, women in increasing tertiles of polyunsaturated fat intake were somewhat more likely to use vitamin E supplements.

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Table 3—Mean differences in change in cognitive function scores, by tertile of dietary fat intake after diabetes diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P_trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat (median intake)*</td>
<td>7.7</td>
<td>10.1</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>0.00 (ref)</td>
<td>-0.09 (-0.18 to 0.0006)</td>
<td>-0.18 (-0.29 to -0.06)</td>
<td>0.003</td>
</tr>
<tr>
<td>Verbal score</td>
<td>0.00 (ref)</td>
<td>-0.11 (-0.22 to 0.005)</td>
<td>-0.18 (-0.33 to -0.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Monounsaturated fat (median intake)*</td>
<td>9.2</td>
<td>11.6</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>0.00 (ref)</td>
<td>0.06 (-0.03 to 0.15)</td>
<td>0.09 (-0.03 to 0.20)</td>
<td>0.2</td>
</tr>
<tr>
<td>Verbal score</td>
<td>0.00 (ref)</td>
<td>0.05 (-0.06 to 0.16)</td>
<td>0.07 (-0.07 to 0.21)</td>
<td>0.4</td>
</tr>
<tr>
<td>Polyunsaturated fat (median intake)*</td>
<td>4.4</td>
<td>5.5</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>0.00 (ref)</td>
<td>0.06 (-0.02 to 0.14)</td>
<td>0.04 (-0.04 to 0.13)</td>
<td>0.3</td>
</tr>
<tr>
<td>Verbal score</td>
<td>0.00 (ref)</td>
<td>0.06 (-0.04 to 0.15)</td>
<td>0.03 (-0.08 to 0.14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Trans fat (median intake)*</td>
<td>0.9</td>
<td>1.3</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>0.00 (ref)</td>
<td>-0.07 (-0.16 to 0.01)</td>
<td>-0.10 (-0.20 to 0.007)</td>
<td>0.07</td>
</tr>
<tr>
<td>Verbal score</td>
<td>0.00 (ref)</td>
<td>-0.09 (-0.20 to 0.01)</td>
<td>-0.08 (-0.21 to 0.05)</td>
<td>0.2</td>
</tr>
<tr>
<td>Ratio of polyunsaturated to saturated fat (median intake)</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>0.00 (ref)</td>
<td>0.05 (-0.03 to 0.13)</td>
<td>0.07 (-0.008 to 0.16)</td>
<td>0.08</td>
</tr>
<tr>
<td>Verbal score</td>
<td>0.00 (ref)</td>
<td>0.02 (-0.08 to 0.12)</td>
<td>0.06 (-0.04 to 0.17)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data are mean differences (95% CI) unless otherwise indicated. Average diet intake after diabetes diagnosis from diabetes diagnosis through the initial cognitive interview. Models are adjusted for age (continuous), education (registered nurse, bachelor’s, or graduate degree), other fats and cholesterol (intertertiles), total caloric intake (continuous), baseline cognition (continuous), time between cognitive interviews (continuous), BMI (continuous), physical activity (continuous), diabetes medication (none, oral hypoglycemic medication only, insulin use), and duration of diabetes (<5, 5–9, 10–14, and ≥15 years). *Fat intake is expressed as a percentage of total energy consumption.

Decline of 0.02 standard units; thus, the association we observed for high consumption of trans fat was equivalent to ~7 years of cognitive aging, and the observed relation for high saturated fat intake was equivalent to 6 years of cognitive aging.

In contrast, women with higher intake of monounsaturated fat maintained better cognitive function than those with lower intake, although this finding was only borderline significant (P trend = 0.06). Polyunsaturated fat intake, considered alone, was not significantly associated with cognitive decline (P trend = 0.5); however, women with a higher ratio of polyunsaturated to saturated fat intake had significantly lower rates of cognitive decline for the global score (P trend = 0.03). Specifically, compared with women in the lowest tertile of polyunsaturated fat relative to saturated fat intake, those in the highest tertile declined an average of 0.08 standard units less (95% CI 0.008–0.16).

In secondary analyses, results were not substantially different when we adjusted for A1C levels, although P values were higher in the small subset of women with this information. For example, the mean difference in global score was −0.12 standard units before adjustment for A1C versus −0.11 after adjustment, when extreme tertiles of saturated fat were compared.

Substitution models yielded results that were consistent with those given above (data not shown in Table 2); specifically, replacement of 1% of total energy from “bad” fat (saturated and trans unsaturated) with the same percentage of energy from “good” fat (mono- and polyunsaturated) was associated with significantly less cognitive decline. For example, for a 5% substitution, the mean difference in global score decline was 0.15 standard units (95% CI 0.005–0.30). That is, replacing 5% of energy from bad fat with good fat could be considered cognitively equivalent to delaying aging by ~7 years.

In analyses of diet after diabetes diagnosis, women had an average of 9 years between diagnosis and initial cognitive interview. Relations of postdiabetes fat intake and cognitive decline were similar to those observed when we considered diet since midlife (Table 3). Increasing intake of saturated fat was related to worse cognitive decline across global (P = 0.003) and verbal scores (P trend = 0.02). Specifically, women in the highest tertile of saturated fat intake had worse cognitive effects we find for 6–7 years of aging in these women. Importantly, these results were consistent with the pathogenesis of both diabetes and cognitive decline, including well-recognized pre-diabetic changes in insu-
lin and lipid regulation, and the long preclinical phase associated with cognitive decline. To our knowledge, this is the first large-scale prospective study to examine dietary fat intake in relation to cognitive decline among type 2 diabetic subjects. Limited previous studies have yielded inconsistent results on the association of dietary fat intake and cognitive decline in healthy subjects (20), but several lines of evidence suggest that dietary fat modification may have a more compelling rationale in diabetic subjects. Higher intakes of saturated and trans fat and lower intakes of mono- and polyunsaturated fat can contribute to insulin resistance and an atherogenic lipid profile (21). Moreover, insulin resistance, high insulin levels, and cholesterol are all implicated in β-amyloid accumulation in the brain—the pathologic hallmark of Alzheimer's disease (22). In type 2 diabetic subjects, replacement of saturated fat with mono-unsaturated fat is associated with improvements in glucose and lipid metabolism (23), and higher intake of saturated fat, or lower intake of polyunsaturated fat relative to saturated fat, elevates the risk of cardiovascular disease (4)—a condition that has been consistently linked to an increased risk of cognitive decline (24).

This study has several limitations. First, self-reported dietary information can lead to random misclassification and underestimation of associations in a prospective study. However, we averaged repeated dietary measures, which decreases random error. Differential bias may have occurred if the diagnosis of diabetes led to dietary changes; however, our results were similar for pre- and post-diabetes fat intake, including models with simultaneous adjustment for these intake periods. Additional adjustment for several comorbid conditions common in diabetic subjects (which could also be confounding variables related to dietary habits) also did not change our results. Furthermore, if subjects with poorer health or more comorbid conditions were most motivated to adopt better dietary habits, this would tend to bias our results toward the null and would not explain the strong relations we found between fat intake and cognition.

Most importantly, this was an observational study, and therefore we cannot rule out the possibility of confounding. However, we found robust results over long follow-up periods and considered confounding by a wide range of health and lifestyle factors. We studied a homogeneous cohort of well-educated female health professionals, which minimizes confounding by health knowledge and access to health care. Still, confounding by diabetes severity and control remains a possible concern. Although we do not have information on diabetes control from all women, we used key proxy measures—diabetes medication and duration of diabetes—since they are likely important indicators of disease status and both have been associated with cognitive function (25). In a small subset of women, we had information on A1C levels available as part of other research in the Nurses’ Health Study. First, we found a very strong relation between these A1C levels and use of diabetes medications (data not shown), suggesting that adjustment for self-reported use of diabetic medications may provide reasonable adjustment for disease severity. Moreover, in a small sample of these women, adjustment for A1C status did not affect the relations we observed between dietary fat and cognitive decline. Nonetheless, confounding cannot be ruled out in an observational study, and our results should be interpreted with caution.

In conclusion, we found that higher long-term intakes of saturated and trans fat were associated with substantially worse cognitive decline in women with type 2 diabetes, but substituting mono- or polyunsaturated fat for these fats was related to reduced cognitive decline. Further research is needed to confirm these findings and explore additional strategies for maintaining cognitive health in diabetics—especially in women, who have a higher lifetime prevalence of both type 2 diabetes and cognitive impairments than men.

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No potential conflicts of interest relevant to this article were reported.

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References

15. Baddeley AD, Bressi S, Della Sala S, Logie R, Spinnler H. The decline of work-
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