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

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ELIZABETH E. DEVORE, SCD[1,2,3]
MEIR J. STAMPFER, MD[1,2,3,4]
MONIQUE M.B. BRETELER, MD[5]
BERNARD ROSNER, PHD[1,2]
JAE HEE KANG, SCD[1,2]
OLIVIA OKEREKE, MD[1,2]
FRANK B. HU, MD[1,2,4]
FRANCINE GRODSTEIN, SCD[1,2,3]

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.

From the [1]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; the [2]Harvard Medical School, Boston, Massachusetts; the [3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the [4]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; and the [5]Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, the Netherlands.
Corresponding author: Elizabeth E. Devore, nheed@channing.harvard.edu.
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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-

ery 4 years thereafter. Foods were specified using a common unit or portion size (e.g., one slice of bread or one 8-oz glass of milk), and detailed information was collected on type of fat or oil used in food preparation. Women reported how often on average they had consumed each item during the previous year, with nine response categories ranging from "almost never" to "six or more times per day." For each food, the reported frequency of consumption was multiplied by its nutrient content (specified in the Harvard University Food Composition Database and updated regularly). Fat intakes were then summed across all food sources and converted to nutrient densities, reflecting intake as a percentage of total energy consumed. We considered the following fat types: saturated, monounsaturated, polyunsaturated, *trans*-unsaturated, and the ratio of polyunsaturated to saturated fat.

In a validation study (9), we determined that dietary fat intake was ascertained reasonably well compared to four 1-week dietary records collected over 1 year. For example, correlation coefficients between the two methods were 0.59 for saturated fat, 0.48 for polyunsaturated fat, and 0.53 for total fat. For *trans* fat, the correlation between our values and *trans* fat composition in adipose tissue was 0.51 (10).

Population for analysis

For this study, we excluded women who did not report dietary information on the initial food frequency questionnaire in 1980 ($n = 330$). We analyzed 1,486 remaining women with type 2 diabetes as of their initial cognitive assessment. The subset of women we excluded was comparable to the study population; for example, their mean age was identical (74.3 years) and average BMI was very similar (28.8 vs. 29.2 kg/m^2).

Cognitive assessment

Initially, we administered the Telephone Interview of Cognitive Status, a telephone adaptation of the Mini-Mental State Examination, which is highly correlated to the Mini-Mental State Examination ($r = 0.94$) (11). After high participation rates were established, we gradually added five other tests: East Boston Memory Test–immediate and delayed recalls (12), category fluency (13,14), delayed recall of 10-word list, and digit span backward (15). Trained nurses administered the cognitive interview and were unaware of participants' dietary fat intake. Interinterviewer reliability was high across 10 interviewers ($r > 0.95$ for each cognitive test). In a validation study, our cognitive battery was administered to 61 highly educated women and correlated well with detailed in-person interviews ($r = 0.81$). Finally, participation rates were identical across all cognitive tests and remained stable over time.

Our analyses focused on measures of global cognition and verbal memory. For global cognition, we averaged together all six cognitive tests. Because a point on each test is not equivalent, we created *z* scores by taking the difference between each participant's score and the population mean score and dividing by the population SD. For verbal memory (a strong predictor of developing Alzheimer's disease [16–18]), we averaged together four tests: immediate and delayed recalls of the East Boston Memory Test and Telephone Interview of Cognitive Status 10-word list. Both composite scores were constructed only for women who completed all contributing tests.

Statistical analysis

Because pathology underlying both diabetes and cognitive decline is likely initiated many years before clinical disease, dietary habits since midlife may be most important (19); thus, our primary predictor was fat intake since midlife, calculated as the average reported from 1980 through the last dietary assessment before initial cognitive interview. However, to specifically consider diet after diabetes diagnosis, especially since women may have changed their diet in response to the diagnosis, we separately averaged fat intake beginning after diabetes diagnosis.

Multivariate-adjusted linear regression models were used to obtain mean differences in cognitive decline across tertiles of fat intake. The 95% CIs were calculated, and linear trend tests were performed using the median value of each tertile. We considered many potential confounders: age, education, depression (based on self-reported use of antidepressant medication), vitamin E supplement use, alcohol intake, physical activity (based on a validated physical activity questionnaire), smoking status, use of cholesterol-lowering medications, and history of high blood pressure, high cholesterol, or myocardial infarction.

Of these, we retained age, education, and physical activity because their inclusion changed effect estimates by >10%. Additionally, in all models, we adjusted for indicators of diabetes severity that had particular potential to confound our results (BMI, disease duration, and treatment). We also included baseline cognitive score, time between cognitive interviews, and total caloric intake in models, as well as each type of dietary fat and cholesterol intake. These covariates were derived from participants' status at the time of initial cognitive assessment (except dietary covariates, which are cumulative averages). In a small subset of women ($n = 404$) with information available, we further adjusted for A1C levels reported near the time of initial cognitive interview.

In addition, because reducing one type of fat without substituting another is difficult, we additionally evaluated "substitution" models that included continuous terms for intakes of "good" fat (the total of mono- and polyunsaturated fat), "bad" fat (the total of saturated and *trans* fat), cholesterol, and protein. By excluding carbohydrates from the model, we could interpret the results as the effect of replacing 1% of energy from carbohydrates with an equivalent percentage of energy from the fat group of interest. We subtracted model coefficients for "good fat" and "bad fat" to determine the effect of replacing one type of fat with the other.

Finally, we had preliminary data from a third cognitive interview; however, the trajectory of cognitive decline across the three interviews was nonlinear (because of an expected learning effect between the first and second interviews). Therefore, these data were more complex to model. In these preliminary analyses, we used general linear models of response profiles and modeling time with indicator variables for assessment rather than with a linear variable. These models are more difficult to interpret and are less powerful, since associations are estimated for each data collection point separately, rather than estimated linearly over time. All analyses were performed in SAS, version 9, software (Cary, NC).

RESULTS — 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* fat were slightly less likely to take vitamin E supplements and had slightly higher preva-

Table 1—*Characteristics of women at initial cognitive assessment, by tertile of dietary fat intake since midlife*

	Saturated fat			Polyunsaturated fat			*Trans* fat		
	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Mean age (years)	75	74	74	74	74	74	75	74	74
Education (% registered nurse degree)	78	78	82	78	82	79	76	81	82
Antidepressant use (%)	8	6	7	7	7	6	7	8	6
Vitamin E supplements (%)	53	50	41	44	49	52	55	48	42
No alcohol intake (%)	68	68	74	70	70	70	68	67	76
BMI ≥30 kg/m^2 (%)	33	39	40	35	38	39	34	37	41
Former smokers (%)	48	46	47	47	48	46	51	48	42
Current smokers (%)	3	6	7	6	5	5	4	5	7
Median physical activity (METs per week*)	8	5	4	5	6	6	7	6	5
History of high blood pressure (%)	78	74	79	78	76	77	75	78	77
History of high cholesterol (%)	81	78	69	77	76	76	79	76	74
History of myocardial infarction (%)	16	15	12	16	15	12	16	16	11
Median diabetes duration (years)	10	8	9	10	9	9	10	9	8
Oral hypoglycemic use (%)	30	34	37	32	34	35	32	36	33
Insulin use (%)	14	14	16	17	13	14	16	15	13

Percentages are of nonmissing values. Average diet intake since midlife from 1980 through the initial cognitive interview. *One metabolic equivalent hour (MET) is proportional to the amount of energy expended sitting quietly.

lence of obesity and current smoking. Women with higher saturated fat intake were also somewhat less likely to exercise and have a history of hypercholesterolemia (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.

For diet since midlife, we found significantly worse cognitive decline on the global score with increasing intakes of saturated (P trend = 0.02) 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

Table 2—*Mean differences in change in cognitive function scores, by tertile of dietary fat intake since midlife*

	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Saturated fat (median intake)*	9.8	11.5	13.5	
Global score	0.00 (ref)	−0.006 (−0.09 to 0.08)	−0.12 (−0.22 to −0.01)	0.02
Verbal score	0.00 (ref)	−0.02 (−0.12 to 0.09)	−0.09 (−0.22 to 0.05)	0.2
Monounsaturated fat (median intake)*	10.6	12.6	14.6	
Global score	0.00 (ref)	0.10 (0.01 to 0.19)	0.12 (−0.002 to 0.24)	0.06
Verbal score	0.00 (ref)	0.06 (−0.05 to 0.17)	0.08 (−0.07 to 0.23)	0.3
Polyunsaturated fat (median intake)*	4.7	5.6	6.7	
Global score	0.00 (ref)	0.03 (−0.04 to 0.11)	0.03 (−0.06 to 0.11)	0.5
Verbal score	0.00 (ref)	0.02 (−0.08 to 0.11)	0.02 (−0.09 to 0.13)	0.7
Trans fat (median intake)*	1.2	1.6	2.0	
Global score	0.00 (ref)	−0.09 (−0.17 to −0.01)	−0.15 (−0.24 to −0.06)	0.002
Verbal score	0.00 (ref)	−0.10 (−0.20 to 0.0002)	−0.15 (−0.27 to −0.03)	0.01
Ratio of polyunsaturated to saturated fat (median intake)	0.4	0.5	0.6	
Global score	0.00 (ref)	0.04 (−0.03 to 0.11)	0.08 (0.008 to 0.16)	0.03
Verbal score	0.00 (ref)	0.04 (−0.05 to 0.14)	0.07 (−0.03 to 0.16)	0.2

Data are mean differences (95% CI) unless otherwise indicated. Average diet intake since midlife from 1980 through the initial cognitive interview. Models are adjusted for age (continuous), education (registered nurse, bachelor's, or graduate degree), other fats and cholesterol (in tertiles), 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.

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

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

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 (in tertiles), 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 declined an average of 0.18 standard units more in the global score than those in the lowest tertile (95% CI −0.29 to −0.06). We also found that women with higher intake of *trans* fat had worse decline on the global score (*P* trend = 0.07), a finding that was borderline significant. As anticipated, average *trans* fat intake in these analyses of more recent diet was lower (by 19%) than in analyses of diet since midlife. In addition, a higher polyunsaturated fat–to–saturated fat ratio was related to better maintenance of cognition; this relation was also borderline significant (*P* trend = 0.08). Finally, results were similar in models that simultaneously included separate terms for fat intake before and after diabetes diagnosis, indicating that diet could be equally important during the period before and after clinical diagnosis of diabetes.

In preliminary analyses of decline over three cognitive assessments, we found results consistent with those reported above. Greater intakes of saturated and *trans* fat were associated with worse cognitive decline for both global and verbal scores, although not all trends were statistically significant (e.g., for *trans* fat, *P* trend = 0.2 for the global score and *P* trend = 0.05 for the verbal score).

CONCLUSIONS — In women with type 2 diabetes, we found that higher intakes of saturated and *trans* fat were related to substantially worse cognitive decline. Furthermore, substitution of saturated and *trans* fat with mono- or polyunsaturated fat was associated with less cognitive decline. The magnitude of these results was considerable, and the associations we observed were equivalent to the cognitive effects we find for 6–7 years of aging in these women. Importantly, these relations were similar before and after diabetes diagnosis; this is 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 monounsaturated 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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