Sex-related differences in cognitive trajectories in older individuals with type 2 diabetes and overweight or obesity

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Abstract

Introduction: It is unknown whether rates of cognitive decline differ between older women and men with type 2 diabetes (T2D) and overweight or obesity.

Methods: Two to four cognitive assessments were obtained across up to 10 years from 2799 adults (mean age 68 years; 62% women) with T2D who had been enrolled in a clinical trial of weight loss intervention. Sex-related differences in means and rates of decline of cognitive scores were assessed.

Results: Women outperformed men in verbal learning and processing speed ($P < 0.001$), but not executive function ($P = 0.22$). The rates of decline over time for women and men were similar ($P \geq 0.10$); however women, but not men, with apolipoprotein E (APOE) ε4 alleles had steeper declines in verbal learning ($P = 0.02$) and processing speed ($P = 0.007$) than those without these alleles.

Discussion: Cognitive advantages for women with T2D and overweight/obesity over men are preserved as they age; however, these are eroded by the APOE ε4 genotype.

KEYWORDS
apolipoprotein E ε4, cognitive decline, obesity, sex, type 2 diabetes mellitus
1 | BACKGROUND

Numerous studies have reported that women’s cognitive performance, particularly in the domains of verbal learning and memory, exceeds that of men’s throughout adulthood, and some have reported that their rates of cognitive decline, as they age, tend to be less steep.1–4 However, sex-related differences in cognitive decline may vary depending on a number of characteristics including the presence of risk factors, the frequency with which they occur in either sex, and the strength of risk factor relationships.5 For example, although there is a higher prevalence of diabetes and insulin resistance in men,6,7 these conditions may more adversely affect cardiovascular and brain health in women compared to men.8,9 Obesity, as well as diabetes, is known to increase rates of cognitive decline in older cohorts.9–13 It is not known, however, whether rates differ between women and men with these two conditions and whether the presence of apolipoprotein E (APOE) ε4 alleles, which may more adversely affect cognitive function among women than men,4,14 particularly in the domains of verbal learning and memory, alters any sex-related differences in such individuals.

We have previously reported, using cross-sectional data from the large Action for Health in Diabetes (Look AHEAD) cohort with diabetes and obesity, that women had better mean performances than men on tests of verbal learning and memory, attention, and global cognitive function, but similar performances on executive function.15 To our surprise, we also found that the prevalence of centrally adjudicated cognitive impairment (either mild cognitive impairment [MCI] or dementia) was 45% lower among women than men and that this difference remained constant throughout the entire age range of the cohort, from 55 to 86 years. This prior cross-sectional analysis could not distinguish whether this resulted from a slower rate of cognitive aging in women versus men, from relative cognitive benefits having emerged prior to cognitive assessments, or perhaps both. We now have available longitudinal assessments of cognitive functions across up to 10 years in this cohort. We use these to compare the trajectories of cognitive changes over time between women and men to address the questions left unanswered by our prior cross-sectional analysis. Secondarily, we looked to see if any differences between sexes were attenuated among APOE ε4 allele carriers, based on finding evidence for this cross-sectionally.

2 | METHODS

The design and methods of Look AHEAD have been published previously,16 as have its CONSORT diagram and primary results.17 It was a randomized controlled trial that recruited 5145 individuals (during 2001 to 2004) who had overweight or obesity and type 2 diabetes mellitus (T2DM). At enrollment, participants were ages 45 to 76 years and had body mass index (BMI) > 25 kg/m² (> 27 kg/m² if on insulin), glycated hemoglobin (HbA1c) < 11%, systolic/diastolic blood pressure < 160/100 mmHg, and triglycerides < 600 mg/dL, per protocol. Prior to enrollment, each prospective participant completed a 2-week run-in, successfully recording information each day about diet and physical activity, and passed a maximal exercise stress test. In addition, each met with a behavioral psychologist or interventionist to confirm understanding of intervention requirements and to exclude those with significant competing life stressors or other issues (depression, alcohol abuse) that might impair adherence.

Participants provided written informed consent. Local institutional review boards approved protocols.

2.1 | Interventions

Participants were randomly assigned with equal probability to Intensive Lifestyle Intervention (ILI) or Diabetes Support and Education (DSE) Please correct: should be Diabetes Support and Education. The multidomain ILI targeted reducing caloric intake and increasing physical activity to induce weight loss to average ≥ 7% at year 1 and maintain this over time.18 It also targeted improved diet (< 30% calories from fat, < 10% calories from saturated fat, ≥ 15% calories from protein) and provided annual monitoring of cardiometabolic risk factors (lipids, glycosylated hemoglobin, and blood pressure).

DSE participants were invited to attend three group sessions each year that focused on diet, physical activity, and social support.19 They did not receive specific diet, activity, or weight goals or information on behavioral strategies, but had similar cardiometabolic risk factor monitoring as ILI participants.

Interventions were terminated in September 2012. The mean (range) lengths of the intervention period for ILI and DSE participants in this article were both 9.8 (8.4, 11.1) years.

2.2 | Cognitive function

Centrally trained, certified, and masked staff conducted standardized assessments of cognitive function in the full Look AHEAD
cohorts (N = 3750) between August 2013 and December 2014, 10 to 13 years after their Look AHEAD enrollment. A subset (N = 1578) had one or two earlier assessments in the Look AHEAD Movement and Memory Study (4 clinics; years 8–11) and the Look AHEAD Brain MRI study (three clinics; years 10–12). Cognitive assessments were repeated in 15 clinics in 2018–2020, 16 to 18 years after enrollment, in the Look AHEAD MIND ancillary study (N = 2451).

To assess changes in cognition, we limited our analysis to the 2799 participants who had at least two (and up to four) cognitive assessments during follow-up. This included 2450 participants from Look AHEAD MIND and 349 who were not assessed during Look AHEAD MIND but who had prior repeated assessments.

The same cognitive battery was used for all cognitive assessments. For this analysis, we focused on the following cognitive domains. Verbal memory was defined as the mean of z-scores from the Rey Auditory Verbal Learning Test (RAVLT) immediate and delayed tasks. Executive function was defined as the mean of z-scores from the Modified Stroop Color and Word Test (MSCWT) and the Trail Making Test-Part B (TMT-B). Processing speed was based on the Digit Symbol Coding test (DSC). We report results for these three domains and the cognitive composite score, the average scores adopted by Look AHEAD MIND for its primary outcome, which was based on scores from the full battery.

2.3 Assessment of risk factors for cognitive decline

Certified clinic staff, masked to intervention assignment, collected data. Sex and diabetes duration were based on self-report at the time of enrollment. Digital scales were used throughout follow-up to obtain annual measures of weight. Blood pressure was measured annually using an automated device and standard protocols. Depression symptoms were assessed with the Beck Depression Index–BDI-2. Participants brought current prescription medications to update medication records. Blood specimens were collected after a 12-hour fast and analyzed centrally for HbA1c. TaqMan genotyping for APOE ε4 (i.e., the rs7412 and rs429358 alleles) was performed. Participants were classified as APOE ε4 carriers if they were homozygous or heterozygous for the APOE ε4 allele.

2.4 Statistical analysis

We compared distributions of risk factors for cognitive decline between women and men using t-tests and analyses of covariance. Sex-related differences in cognitive function tests were assessed using t-tests and sex-related differences in the composite cognitive outcomes defined above were assessed using analyses of covariance. Mixed effects models were used to assess differences in the slopes of longitudinal cognitive assessments over follow-up time. We included age, education, race/ethnicity, time since enrollment, number of prior assessments (to control for learning effects), and clinical site as covariates in analyses. We also included intervention assignment, although mean cognitive function and rates of decline did not significantly vary between the two intervention groups for any of the cognitive domains we assessed. Interaction terms were included in models to examine the consistency of relationships between carriers and non-carriers of the APOE ε4 allele.

To gauge the sensitivity of our findings to biases associated with differential follow-up, we used inverse probability modeling. This involved fitting logistic regression models to generate fitted probabilities, from logistic regression with factors from Table 1, in which the dependent variable was whether the individual had more than one cognitive assessment. We repeated the main analyses, weighting these with the inverse of these fitted probabilities, and compared these to the unweighted analyses.

3 RESULTS

Table 1 contrasts the characteristics of participants at their assessment most proximal to the first of administration of the Look AHEAD cognitive battery. Included are 2799 individuals who contributed two to four cognitive assessments (mean 2.4 for both sexes) over an average of 5.5 years, which was the same for both sexes. Women and men tended to differ according to many risk factors for cognitive decline. Those that might be expected to decrease risk for women were younger age, lower diastolic blood pressure, and less use of statins (an indication of dyslipidemia). Those expected to increase risk were less education, greater numbers of racial/ethnic minorities, greater BMI, higher systolic blood pressure, and more use of antidepressants. Assignment to the interventions was balanced between women and men; however, women lost a greater percentage of weight after randomization.

Table 2 lists covariate-adjusted mean standardized cognitive domain scores for women and men at the initial cognitive assessment. Women had significantly better scores for the domains of verbal learning and processing speed (both P < 0.001), but not executive function. They also significantly outperformed men for the overall composite cognitive function. Also included in Table 2 are mean slopes over time: for these, there were no significant differences; that is, the rates of cognitive decline were similar for women and men.

Table 3 provides parallel results for women and men additionally grouped by presence (yes/no) of APOE ε4 alleles. Overall, at the initial cognitive assessment, mean scores were not different between the genetic groups for both women and men: 95% confidence intervals (CIs) for mean differences did not exclude 0 for any domain. There were also no significant interactions between genotype and sex for scores at the initial cognitive assessment.

Also included in Table 3 are mean slopes by genotype. For women, APOE ε4 alleles were associated with increased rates of cognitive decline for all three domains: 95% CIs uniformly excluded 0. For men, this difference was only marginally evident for executive function, and was not statistically significant. For both verbal learning (P = 0.02) and processing speed (P = 0.007) there were significant differences in the
| Characteristic                              | Women N = 1742 | Men N = 1057 | P-value |
|-------------------------------------------|----------------|--------------|---------|
| Age, years                                | 67.1 (6.2)     | 68.5 (6.3)   | <0.001  |
| Diabetes duration, years                  | 16.5 (6.5)     | 16.5 (5.9)   | 0.91    |
| Education                                 |                |              | <0.001  |
| High school graduate                      | 1118 (64.2%)   | 451 (42.7%)  |         |
| College graduate                          | 322 (18.5%)    | 289 (27.3%)  |         |
| Post college education                    | 248 (14.2%)    | 303 (28.7%)  |         |
| Other                                     | 54 (3.1%)      | 14 (1.3%)    |         |
| Race/ethnicity                            |                |              | <0.001  |
| Black                                     | 343 (19.7%)    | 113 (10.7%)  |         |
| American Indian                           | 139 (8.0%)     | 37 (3.5%)    |         |
| Hispanic/Latino                           | 293 (16.8%)    | 92 (8.7%)    |         |
| White                                     | 916 (52.6%)    | 783 (74.1%)  |         |
| Other, multiple                           | 51 (2.9%)      | 32 (3.0%)    |         |
| Body mass index, kg/m²                    | 34.6 (6.4)     | 33.7 (5.7)   | <0.001  |
| HbA1c, %                                  | 7.42 (1.54)    | 7.31 (1.39)  | 0.07    |
| Blood pressure, mmHg                      |                |              | <0.001  |
| Systolic                                  | 127.8 (18.8)   | 125.3 (17.4) |         |
| Diastolic                                  | 65.0 (9.5)     | 67.9 (8.9)   |         |
| Medications                               |                |              |         |
| Insulins                                  | 546 (32.4%)    | 348 (32.9%)  | 0.76    |
| Statins                                   | 1148 (65.9%)   | 803 (76.0%)  | <0.001  |
| Antidepressants                           | 403 (23.2%)    | 190 (18.1%)  | 0.001   |
| APOE ε4 alleles (Missing = 496)           |                |              | 0.65    |
| 0                                         | 1073 (76.8%)   | 706 (78.0%)  |         |
| 1                                         | 302 (21.6%)    | 182 (20.1%)  |         |
| 2                                         | 23 (1.6%)      | 17 (1.9%)    |         |
| Intervention assignment                   |                |              | 0.99    |
| Diabetes support and education            | 849 (48.7%)    | 515 (48.7%)  |         |
| Intensive lifestyle intervention          | 893 (51.3%)    | 542 (51.3%)  |         |
| Time between randomization and first cognitive assessment, years | 10.3 (1.6) | 10.1 (1.7) | 0.006 |
| Percent weight change from randomization at first cognitive assessment | -4.3 (10.5) | -2.9 (9.3) | <0.001 |
| Cognitive test scores                     |                |              |         |
| Modified Mini-Mental                      | 92.0 (6.5)     | 92.1 (5.8)   | 0.49    |
| AVLT Immediate                            | 43.4 (8.6)     | 38.4 (8.3)   | <0.001  |
| AVLT Delayed                              | 8.3 (3.2)      | 6.5 (3.0)    | <0.001  |
| Stroop                                    | 33.1 (15.2)    | 32.5 (15.0)  | 0.31    |
| Digit Symbol Coding                       | 41.0 (11.1)    | 39.8 (9.8)   | 0.005   |
| Trails-A<sup>a</sup>                      | 38.5 (17.4)    | 36.7 (14.9)  | 0.009   |
| Trails-B<sup>a</sup>                      | 110.4 (69.0)   | 102.0 (60.4) | 0.001   |

<sup>a</sup>Higher scores reflect poorer performance.

<sup>*</sup>mean (standard deviation) or N (percent)

Abbreviations: APOE, apolipoprotein E; AVLT, Auditory Verbal Learning Test; HbA1c, glycated hemoglobin.
### TABLE 2
Mean standardized scores at initial exam and slopes (units/year) and standard errors by sex, with covariate adjustment for age, education, race/ethnicity, randomization assignment, time since enrollment, and clinical site

| Variable               | Mean (SE) initial cognitive assessment [95% CI] | Slopes*: Mean (SE) SD/year [95% CI] |
|------------------------|-----------------------------------------------|------------------------------------|
|                        | Mean | SD | P-values | Mean | SD | P-value |
| Cognitive domains      | Women | Men |          | Women | Men |          |
| Verbal learning        | 0.22 (0.02) | -0.40 (0.03) | <0.001 | -0.090 (0.007) | -0.083 (0.008) | 0.16 |
|                        | [0.19, 0.26] | [-0.44, -0.35] |          | [-0.104, -0.077] | [-0.098, -0.067] |          |
| Executive function     | -0.07 (0.02) | -0.11 (0.02) | 0.22 | -0.070 (0.007) | -0.069 (0.007) | 0.92 |
|                        | [-0.11, -0.03] | [-0.16, -0.06] |          | [-0.084, -0.056] | [-0.084, -0.056] |          |
| Processing speed       | 0.01 (0.02) | -0.27 (0.03) | <0.001 | -0.091 (0.006) | -0.084 (0.006) | 0.10 |
|                        | [-0.03, 0.05] | [-0.32, -0.22] |          | [-0.102, -0.079] | [-0.096, -0.072] |          |
| Composite              | 0.03 (0.01) | -0.20 (0.02) | <0.001 | -0.081 (0.004) | -0.077 (0.005) | 0.20 |
|                        | [0.01, 0.06] | [-0.23, -0.16] |          | [-0.090, -0.072] | [-0.086, -0.068] |          |

*With additional covariate adjustment for any differences in slopes among age and randomization assignment groups and also number of prior assessments (i.e., to control for learning effects).

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error.

### TABLE 3
Mean standardized scores at initial exam and slopes (units/year) and standard errors by sex and APOE ε4 status, with covariate adjustment for age, education, race/ethnicity, randomization assignment, time since enrollment, clinical site, and number of prior assessments

| Variable               | Mean (SE) initial cognitive assessment | Slopes*: Mean (SE) SD/year |
|------------------------|---------------------------------------|----------------------------|
|                        | Women | Men | Interaction | P-value | Women | Men | Interaction | P-value |
| Cognitive domains      |      |     |             |         |       |     |             |         |
| Verbal learning        |      |     |             |         |       |     |             |         |
| No ε4 alleles          | 0.25 (0.02) | -0.36 (0.03) | 0.56 | -0.089 (0.008) | -0.087 (0.008) | 0.02 |
|                        | [0.19, 0.26] | [-0.44, -0.35] |          | [-0.104, -0.077] | [-0.098, -0.067] |          |
| 1–2 ε4 alleles         | 0.20 (0.04) | -0.36 (0.06) |          | -0.119 (0.010) | -0.084 (0.012) |          |
|                        | [0.17, 0.25] | [-0.41, -0.31] |          | [-0.101, -0.091] | [-0.094, -0.078] |          |
| Executive function     |      |     |             |         |       |     |             |         |
| No ε4 alleles          | -0.06 (0.02) | -0.08 (0.03) | 0.39 | -0.069 (0.008) | -0.071 (0.009) | 0.54 |
|                        | [-0.10, -0.02] | [-0.12, -0.04] |          | [-0.080, -0.050] | [-0.082, -0.050] |          |
| 1–2 ε4 alleles         | -0.03 (0.02) | -0.11 (0.05) |          | -0.089 (0.010) | -0.082 (0.012) |          |
|                        | [-0.07, -0.09] | [-0.15, -0.07] |          | [-0.099, -0.069] | [-0.101, -0.069] |          |
| Processing speed       |      |     |             |         |       |     |             |         |
| No ε4 alleles          | 0.03 (0.02) | -0.21 (0.03) | 0.06 | -0.092 (0.006) | -0.090 (0.007) | 0.007 |
|                        | [-0.03, 0.09] | [-0.29, -0.13] |          | [-0.099, -0.080] | [-0.101, -0.081] |          |
| 1–2 ε4 alleles         | 0.07 (0.04) | -0.33 (0.06) |          | -0.114 (0.008) | -0.084 (0.009) |          |
|                        | [-0.03, 0.17] | [-0.40, -0.26] |          | [-0.096, -0.066] | [-0.104, -0.067] |          |
| Composite              |      |     |             |         |       |     |             |         |
| No ε4 alleles          | 0.06 (0.02) | -0.15 (0.02) | 0.54 | -0.080 (0.005) | -0.079 (0.005) | 0.08 |
|                        | [0.03, 0.10] | [-0.21, -0.09] |          | [-0.080, -0.069] | [-0.079, -0.069] |          |
| 1–2 ε4 alleles         | 0.05 (0.03) | -0.20 (0.04) |          | -0.102 (0.006) | -0.087 (0.007) |          |
|                        | [0.02, 0.08] | [-0.26, -0.14] |          | [-0.101, -0.081] | [-0.103, -0.082] |          |

Abbreviations: APOE, apolipoprotein E; SD, standard deviation; SE, standard error.

*95% confidence interval excludes 0.

Associations between genotype and cognitive decline between women and men. Supplement S1 in supporting information portrays mean differences in verbal learning scores between sexes (women minus men) across the up to four longitudinal assessments, separately for APOE ε4 non-carriers and carriers. These have been adjusted for time between assessments, education, race/ethnicity, clinical site, and intervention assignment. P-value was based on tests for gradients across assessments. For non-carriers, the cognitive advantages that women demonstrated relative to men were maintained across assessments. For carriers, these advantages attenuated across follow-up.

Supplement S2 in supporting information compares the participants included in our analyses; that is, those who had two to four longitudinal assessments, with participants who only had one (and thus were lost due to attrition). Individuals who were lost to follow-up (N = 1138;...
29.9%) tended to be older and to have worse health profiles and poorer scores on cognitive function tests, except for the Stroop test. Men had slightly higher attrition rates (31.1%) compared to women (27.5%). Supplement S3 in supporting information parallels Table 2, presenting results from analyses with inverse probability weights. These weights, which assign greater influence to participants who were similar to those who were lost to follow-up, yielded lower mean cognitive function scores, as would be expected, but comparable sex-related differences. We also repeated analyses underlying Table 3 using inverse probability weighting. These results were very similar to those in Table 3, with one exception. For composite cognitive function, among women the mean (standard error) slope for APOE ε4 non-carriers was $-0.080$ (0.005) and for APOE ε4 carriers it was $-0.108$ (0.006), a mean (95% CI) difference of $0.028$ (0.017,0.040); among men the slope for APOE4 ε4 non-carriers was $-0.083$ (0.005) and for APOE4 ε4 carriers it was $-0.085$ (0.008), a mean (95% CI) difference of $0.002$ ($-0.012,0.016$). The two-way interaction between sex and APOE ε4 alleles was now significant ($P = 0.005$), whereas without inverse probability weighting it was not ($P = 0.08$).

Figure 1 portrays the education- and race/ethnicity-adjusted prevalence of cognitive deficits, which we operationally defined as a composite cognitive function z-score lower than $-1.30$; that is, approximately the tenth percentile of a standard normal distribution. These are arrayed by sex and age group (at the time of the final assessment). While the prevalence of cognitive deficits was greater among older individuals in both sexes, there was a strikingly higher rate among older men (26.9%) compared to older women (16.7%), $P < 0.001$.

### 4 DISCUSSION

Results from these exploratory analyses present three issues for discussion. First, consistent with reports from other cohorts, women in the Look AHEAD trial tended to outperform men with respect to verbal learning and processing speed, but not executive function. Second, there were no differences in the rates of cognitive decline between women and men, suggesting that overall the relative cognitive advantages for women were maintained throughout follow-up. This was evidenced by the greater prevalence of cognitive deficits among men compared to women at their final cognitive assessment. Finally, at the initial cognitive assessment, women’s advantage over men was independent of the APOE ε4 genotype. However, female APOE ε4 carriers had faster rates of decline in verbal learning and processing speed relative to male APOE ε4 carriers, suggesting that cognitive aging was accelerated later in life for women with APOE ε4 rather than men with the allele. Because APOE ε4 is the strongest risk factor for dementia due to Alzheimer’s disease (AD), it is possible that greater underlying AD pathology in women compared to men explains this observation.

There is some evidence that obesity is associated with relatively slower age-related cognitive decline in women compared to men, which may lead to relatively lower risks for cognitive impairment. This may be linked to increased production of endogenous estrogens in adipose tissue, which may protect against neuropathology. We found, however, little difference in the rates of cognitive decline in the Look AHEAD cohort over time. Thus, while the relative advantages evident for women in the domains of memory and processing speed appeared to be largely maintained into later life, which may be associated with their relatively lower risks for cognitive impairment, sex-related differences in performance levels did not appear to expand over time. T2DM is known to differentially increase risks for stroke and cardiovascular disease in women compared to men, and in the Look AHEAD cohort women had greater burdens of cerebrovascular disease than men. Thus, it is possible that increased underlying pathology may have prevented any further expansion of benefits over time. We also examined whether sex-related differences varied with diabetes duration, but found no evidence for such interactions for cross-sectional composite cognitive function ($P = 0.40$) or rates of its change over time ($P = 0.66$).

Another factor may be the APOE ε4 genotype, which differentially increases risks for cognitive impairment in women compared to men, and, in the Look AHEAD cohort, may have attenuated any benefits that its lifestyle intervention may have provided perimenopausal women. We have previously speculated that this may be associated with an adverse interaction between endogenous estrogen and the APOE ε4 genotype on glucose metabolism in the brain, which places T2DM women who are APOE ε4 carriers at greater risk for cognitive impairment relative to non-carriers. The APOE ε4 genotype is associated with lower rates of glucose metabolism in several areas in the brain affected by AD, which may further be compromised by T2DM.

Wang et al., in a cohort grouped according to normal cognition, MCI, and AD found that APOE ε4 genotype was associated with greater declines in verbal memory in women compared to men. This resonates with our finding that declines in memory were more adversely affected among women by the APOE ε4 genotype, compared to men. However, the greater declines were limited to only those with MCI.

It is natural to wonder how our findings may be influenced by differential attrition. While we have demonstrated that attrition was variably related to many characteristics of the Look AHEAD
participants, the sensitivity analyses we conducted, using inverse probability weighting, provide some support that this did not bias our findings. Of the 1138 participants who had only one cognitive assessment during Look AHEAD and thus were included from our analyses, 343 (30.1%) died prior to the end of data collection and 795 did not provide follow-up data for other reasons. Men accounted for 56.0% of the deaths. Of the participants who provided two or more cognitive assessments, and are thus included in this analysis, 143 subsequently died during later follow-up, of which 58.0% were men.

4.1 | Strengths and limitations

As volunteers for a randomized clinical trial of lifestyle intervention, Look AHEAD participants may not reflect general populations. However, our findings may be generalizable to the elderly population with T2DM, which represents more than one quarter of persons 65 years and above in the United States. As noted above, we cannot conclusively rule out that differential attrition may have biased our findings. In addition, differences in the assessment schedules and numbers of tests may have varied across the cohort and potentially added biases.

4.2 | Summary

Women with T2DM and overweight/obesity may maintain their advantages in memory and attention over men into late life. However, the APOE ε4 genotype may attenuate these advantages by differentially accelerating cognitive decline in women with T2DM compared to men. Whether a differential influence of AD pathology by sex explains this finding requires further study.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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