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Featured Article

Sex-related differences in the prevalence of cognitive impairment among overweight and obese adults with type 2 diabetes

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Abstract

Introduction: Type 2 diabetes mellitus and obesity may increase risks for cognitive decline as individuals age. It is unknown whether this results in different prevalences of cognitive impairment for women and men.

Methods: The Action for Health in Diabetes, a randomized controlled clinical trial of a 10-year intensive lifestyle intervention, adjudicated cases of cross-sectional cognitive impairment (mild cognitive impairment or dementia) 10–13 years after enrollment in 3802 individuals (61% women).

Results: The cross-sectional prevalences of cognitive impairment were 8.3% (women) and 14.8% (men): adjusted odds ratio 0.55, 95% confidence interval [0.43, 0.71], $P < .001$. Demographic, clinical, and lifestyle risk factors varied between women and men but did not account for this difference, which was limited to individuals without apolipoprotein E (*APOE*)-ε4 alleles (interaction $P = .034$).

Conclusions: Among overweight and obese adults with type 2 diabetes mellitus, traditional risk factors did not account for the lower prevalence of cognitive impairment observed in women compared with men.

Keywords: Sex differences; Type 2 diabetes mellitus; Obesity; Cognitive impairment

1. Background

In both women and men, type 2 diabetes (T2DM) and midlife overweight and obesity increase long-term risks for cognitive decline and cognitive impairment. Studies disagree, however, whether these effects vary by sex and, if so, whether this may be attributable to differences in risk factor distributions or strengths of risk factor relationships [1–8].

The Action for Health in Diabetes (Look AHEAD) enrolled overweight and obese individuals with T2DM, aged 45–76 years, in a randomized controlled clinical trial of a 10-year multidomain behavioral intervention. When their cognitive impairment status (mild cognitive impairment [MCI] or dementia) was ascertained after intervention,

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its prevalence was 30% lower in women than that in men ($P = .006$) [9]. Here, we explore factors that might account for this striking finding: whether it could be attributed to differences between women and men in demography, lifestyle, medical care, and genotype and whether its magnitude varied across risk factors. We also examined whether markers related to intervention adherence (weight, waist girth, and physical activity) and markers of diabetes treatment and control over time (fasting glucose, glycated hemoglobin (HbA1c), and medications) might have differentially affected risks for cognitive impairment. Identification of sex-specific differences may aid in developing better strategies to prevent cognitive decline and dementia.

2. Methods

The design, CONSORT diagram, and primary results of Look AHEAD have been published [10,11]. It was a single-masked randomized controlled trial that recruited 5145 individuals during 2001–2004 with body mass index (BMI) $>$ 25 kg/m^2 ($>$27 kg/m^2 if on insulin), HbA1c $<$ 11%, systolic/diastolic blood pressure $<$160/100 mm Hg, and triglycerides $<$600 mg/dL. During screening, each participant completed a 2-week run-in, during which they successfully recorded information about diet and physical activity. Each met a behavioral psychologist or interventionist to confirm whether they understood intervention requirements and exclude those with issues likely to 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). The ILI included diet modification and physical activity designed to induce weight loss to average $\geq$ 7% at 1 year and maintain this over time [12]. ILI participants were assigned a daily calorie goal (1200–1800 based on initial weight), with $<$30% of total calories from fat ($<$10% from saturated fat) and $\geq$15% from protein. The physical activity goal was $\geq$175 min/week through activities similar in intensity to brisk walking.

DSE participants were invited (but not required) to attend three annual group sessions focused on diet, physical activity, and social support [13]. They received no specific diet, activity, or weight goals or information on behavioral strategies.

Interventions ended in September 2012. The mean (range) lengths of intervention for ILI and DSE participants reported in this article were both 9.8 (8.4 to 11.1) years.

2.2. Risk factors for cognitive decline

Certified clinic staff, masked to intervention assignment, collected data [10]. Digital scales recoded annual measures of weight. BMI and waist girths were obtained with standard protocols. The Paffenbarger Physical Activity Questionnaire was used to estimate weekly minutes of moderate-to-vigorous physical activity [14]. Participants' current prescription medication use was recorded. At enrollment, women were asked whether they had used hormone therapy previously; however, age at use and its duration were not queried. The Beck Depression Inventory-II assessed depression symptoms [15]. Blood specimens were collected after a $\geq$12-hour fast and analyzed centrally for HbA1c and glucose. A maximal graded exercise test was administered during screening. For participants who provided consent (80% of women; 86% of men, $P < .001$), TaqMan genotyping for apolipoprotein E (*APOE*)-ε4 (the rs7412 allele) was performed.

2.3. Cognitive function

Cross-sectional standardized assessments of cognitive function in the full cohort occurred between August 2013 and December 2014 [16]. The Rey Auditory Verbal Learning Test evaluated verbal learning. The Digit Symbol Coding test evaluated speed of processing and working memory. The modified Stroop Color and Word Test and the Trail Making Test-Part B evaluated executive function. The modified Mini–Mental State Examination evaluated global cognitive functioning. Test results were standardized, using z-scores and ordering so that higher scores reflected better performance [16]. The primary cognitive measure for Look AHEAD was an average of these z-scores (composite cognitive function).

2.4. Cognitive impairment adjudication

A masked expert panel adjudicated cognitive status to identify cognitive impairment and dementia [9]. Participants whose modified Mini–Mental State Examination scores fell below age- and education-specific cutpoints underwent review, which was supplemented by telephone administration of the Functional Assessment Questionnaire to a friend or family member to query functional status and instrumental activities of daily living [17]. Additional cases were identified through adjudicating Functional Assessment Questionnaire scores from participants who had died before cognitive testing.

Two adjudicators independently reviewed all cognitive tests and Functional Assessment Questionnaire scores, and all relevant data (physical function, medications, depression, and hospitalizations) to make their primary classification (no impairment, MCI, and probable dementia), using a successful protocol from other multicenter trials [18]. When MCI was identified, they made a secondary classification of subtype: amnestic single domain, amnestic multidomain, nonamnestic single domain, or nonamnestic multiple domain. Adjudicators used classification of "cannot classify" if they could not make a confident classification.