

Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function

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Background: Few prospective studies have assessed diabetes mellitus as a risk factor for incident Alzheimer disease (AD) and decline in cognitive function.

Objective: To evaluate the association of diabetes mellitus with risk of AD and change in different cognitive systems.

Design: Longitudinal cohort study.

Participants: For up to 9 years, 824 older (those >55 years) Catholic nuns, priests, and brothers underwent detailed annual clinical evaluations.

Main Outcome Measures: Clinically diagnosed AD and change in global and specific measures of cognitive function.

Results: Diabetes mellitus was present in 127 (15.4%) of the participants. During a mean of 5.5 years of obser-

vation, 151 persons developed AD. In a proportional hazards model adjusted for age, sex, and educational level, those with diabetes mellitus had a 65% increase in the risk of developing AD compared with those without diabetes mellitus (hazard ratio, 1.65; 95% confidence interval, 1.10-2.47). In random effects models, diabetes mellitus was associated with lower levels of global cognition, episodic memory, semantic memory, working memory, and visuospatial ability at baseline. Diabetes mellitus was associated with a 44% greater rate of decline in perceptual speed ($P=.02$), but not in other cognitive systems.

Conclusions: Diabetes mellitus may be associated with an increased risk of developing AD and may affect cognitive systems differentially.

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DIABETES MELLITUS IS A common condition in older people, affecting about 20% of persons older than 65 years.¹ In cross-sectional studies,²⁻⁴ diabetes mellitus has been associated with various adverse health effects, including cognitive impairment. The association of diabetes mellitus with impaired cognitive function suggests that diabetes mellitus may contribute to Alzheimer disease (AD). However, few prospective studies have examined the association between diabetes mellitus and incident AD, and their results have been inconsistent, with some studies^{5,6} finding that persons with diabetes mellitus are at increased risk for AD and others^{7,8} not finding this association.

Some studies⁹⁻¹² have examined the relation of diabetes mellitus to change in cognitive function, usually as assessed by a global measure of cognitive function or by a select number of individual cognitive tests. However, little is known about diabetes mellitus and change in different cognitive systems. Such information might provide clues about the basis of the asso-

ciation of diabetes mellitus with AD, as has been the case for other factors associated with the risk of dementia or AD.¹³⁻¹⁵

We used data from the Religious Orders Study, an ongoing longitudinal study of aging and AD in older (those >55 years) Catholic nuns, priests, and brothers, to examine the relation of diabetes mellitus to incident AD and to change in different cognitive abilities. For a mean of 5.5 years, persons underwent annual evaluations, which included the clinical classification of AD and detailed testing of cognitive function, from which preestablished measures of specific cognitive domains were derived. We tested the hypotheses that diabetes mellitus was associated with an increased risk of AD and with more rapid cognitive decline in longitudinal analyses adjusted for selected variables.

METHODS

SUBJECTS

All participants were older Catholic nuns, priests, or brothers who agreed to annual clinical evaluations and brain donation at death. Par-

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Participants were from more than 40 groups across the United States. All participants signed an informed consent and an anatomical gift act donating their brains to Rush investigators at death. The study was approved by the Institutional Review Board of Rush University Medical Center.

Of the 990 persons enrolled in the Religious Orders Study between January 1, 1994, and July 31, 2003, 911 (92.0%) were eligible for this investigation; 79 (8.0%) had dementia at baseline and were excluded from all analyses. Of the 911 participants without dementia, 23 died before the first follow-up evaluation and 41 enrolled in the previous year and had not yet reached the scheduled date of their first follow-up evaluation. This left 847 persons eligible for follow-up; 824 (97.3%) completed at least 1 follow-up. Analyses are based on this group of patients, who underwent a mean of 5.5 clinical evaluations (range, 2-10 evaluations). Missing data have reflected relocation, withdrawal from all or part of the study, and incapacity or unwillingness to complete selected evaluation procedures.

CLINICAL EVALUATION

At baseline, each participant underwent a uniform structured clinical evaluation that followed the procedures recommended by the Consortium to Establish a Registry for Alzheimer's Disease.¹⁶ The evaluation included a medical history, a neurologic examination, neuropsychological performance testing, and a review of a brain scan when available. All prescription and over-the-counter medication names and dosages were recorded after direct inspection of medication containers. A board-certified neuropsychologist (R.S.W.) reviewed the cognitive performance test results. Participants were evaluated in person by a neurologist (Z.A. or D.A.B.) or a geriatrician with expertise in the evaluation of older persons with and without dementia. Based on this evaluation, persons were classified with respect to AD, stroke, and other common conditions with the potential to impact cognitive function. Details of the evaluations have been previously described.^{15,17} The diagnosis of dementia and AD followed the recommendations of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.¹⁸ The diagnosis of clinical stroke was based on review of the medical history, neurologic examination results, and neuroimaging data (brain computed tomography and/or magnetic resonance imaging scans) when available, as previously described.¹⁵ Follow-up evaluations were identical in all essential details to the baseline evaluation, and were performed annually by examiners blinded to previously collected data.

Diabetes mellitus was considered present if the participant was taking a medication to treat diabetes mellitus, reported a history of diagnosis of diabetes mellitus, or both. To increase the accuracy and stability of the identification of this chronic condition, we used diabetes mellitus identified at any evaluation for the primary analyses. All analyses were repeated with diabetes mellitus only identified at the baseline evaluation.

NEUROPSYCHOLOGICAL PERFORMANCE TESTING

Cognitive function tests were selected to assess a broad range of cognitive abilities commonly affected by aging and AD and other dementias, as previously reported.^{17,19,20} The Mini-Mental State Examination was used to describe the cohort, but was not used in analyses. Five cognitive systems, which may be differentially related to risk factors for disease, were assessed using selected neuropsychological tests. Seven tests assessed episodic memory: Word List Memory, Word List Recall, and Word List Recognition from the procedures established by the Consortium to Establish a Registry for Alzheimer's Disease²¹;

immediate and delayed recall of story A from the logical memory subtest of the Wechsler Memory Scale-Revised; and immediate and delayed recall of the East Boston Story. Four tests assessed semantic memory: Verbal Fluency and Boston Naming from the Consortium to Establish a Registry for Alzheimer's Disease, subsets of items from the Extended Range Vocabulary Test, and the National Adult Reading Test. There were 4 tests of working memory: the Digit Span subtests forward and backward of the Wechsler Memory Scale-Revised, Digit ordering, and Alpha span. Two tests were used to assess perceptual speed: the oral version of the Symbol Digit Modalities Test and Number Comparison. Finally, there were 2 tests of visuospatial ability: items from Judgment of Line Orientation and Standard Progressive Matrices. Details regarding the administration of each of these tests have been previously reported.¹⁹ Data were collected on laptop computers with forms programmed in a Pascal-based entry program (Blaise; Central Bureau of Statistics, Voorburg, the Netherlands), and scored using SAS statistical software.²² Crude change per year of individual raw scores was determined by computing the mean difference of the scores between each pair of adjacent annual visits. If one or more annual scores were missing followed by a valid result, we multiplied the difference by the number of years between scores.

Summary measures of each cognitive ability were constructed for use in analyses rather than individual test scores to minimize floor and ceiling effects and other sources of measurement error. We used previously established summary measures^{17,19,20,23} of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability and a summary measure of global cognitive function. Each summary measure was constructed by converting the raw scores from the individual tests to *z* scores, using the mean and standard deviation from the baseline evaluation of all participants, and averaging the *z* scores. The summary measure of global cognitive function was based on 19 tests. Valid summary measures required valid scores on at least half of the component tests. Several studies²⁴⁻²⁶ characterizing cognitive function using this approach in this and other cohorts have been previously reported.

STATISTICAL ANALYSIS

All analyses adjusted for age, sex, and educational level. Cox proportional hazards models were used to estimate the risk of AD among persons with diabetes mellitus compared with those without diabetes mellitus.²⁷

Random effects models were used to test the effects of diabetes mellitus on baseline level of function and annual rate of change (fixed effects) while adjusting for person-specific paths of cognitive change with random effects. In this growth curve approach, each individual's path is assumed to follow the mean path of the group, except for random effects that cause the initial level of function (ie, intercept) to be higher or lower and the rate of change (ie, slope) to be faster or slower.

We constructed separate random effects models for each of the 5 cognitive domain scores and for the global cognitive score. Each model included terms for time (in years since baseline), the presence of diabetes mellitus, and their interaction. The term for time indicates the mean annual change in cognition for those without diabetes mellitus. The term for diabetes mellitus denotes the mean difference in baseline cognition between those with diabetes mellitus and those without it. The interaction term indicates the mean additional annual change in cognition associated with having diabetes mellitus.

Model assumptions were examined graphically and analytically, and were adequately met.

Analyses were performed using SAS statistical software,²² and plots were made with (S-Plus).

RESULTS

Of the 824 participants included in these analyses, diabetes mellitus was present in 127 (15.4%) sometime during the study period; 91 (11.0%) had diabetes mellitus at baseline. Of the 127 persons with diabetes mellitus, 85 (66.9%) were taking medication for the treatment of diabetes mellitus: 15 persons were taking insulin but no oral hypoglycemic agent, 55 were taking an oral hypoglycemic agent but not insulin, and 15 were taking both. Overall, there were more men in the group with diabetes mellitus (**Table 1**).

DIABETES MELLITUS AND RISK OF AD

During the follow-up evaluations, 151 persons developed AD, of whom 31 had diabetes mellitus. In a proportional hazards model adjusted for age, sex, and educational level, there was a 65% increase in the risk of developing AD in those with diabetes mellitus compared with those without diabetes mellitus (hazard ratio, 1.65; 95% confidence interval, 1.10-2.47). The cumulative hazard of AD over time, adjusted for age, sex, and educational level, is shown graphically in **Figure 1** for typical participants with and without diabetes mellitus. Similar results were found in analyses with diabetes mellitus identified at baseline only (hazard ratio, 1.53; 95% confidence interval, 0.96-2.45).

We performed additional analyses of variables with the potential to confound or modify the association between diabetes mellitus and incident AD. Because stroke is associated with diabetes mellitus and dementia, we repeated the analysis with a term added for stroke. Of the 824 participants, 132 (16.0%) experienced 1 or more strokes (at the baseline or follow-up evaluation). The association of diabetes mellitus with AD was not substantially changed after adjusting for stroke (hazard ratio, 1.58; 95% confidence interval, 1.05-2.38). In a subsequent model, we found no evidence for an interaction between diabetes mellitus and stroke ($P = .68$).

DIABETES MELLITUS AND RATE OF COGNITIVE DECLINE

Table 2 shows the mean and standard deviation of the baseline scores and of the crude change per year in scores of individual cognitive test results, according to the presence or absence of diabetes mellitus. To examine the relation of diabetes mellitus to cognitive decline, we used a global measure of cognition, based on individual tests in **Table 2**, and constructed a random effects model controlling for age, sex, and educational level. Compared with persons without diabetes mellitus, persons with diabetes mellitus had lower baseline scores but did not decline significantly faster ($P = .06$) (**Table 2**). A similar result was found in analyses in which diabetes mellitus was identified solely at the baseline evaluation.

Because cognitive function is a multidimensional process and diabetes mellitus may affect some cognitive systems but not others, we next examined the relation of diabetes mellitus to baseline level and change of 5 specific cognitive domains in separate random effects models, controlling for age, sex, and educational level.

Table 1. Characteristics of the 824 Participants, According to the Presence or Absence of Diabetes Mellitus*

Characteristic	Diabetes Mellitus	
	Present (n = 127)	Absent (n = 697)
Age at baseline, y	74.4 (6.1)	75.2 (7.1)
Male sex, No. (%)	57 (44.9)	200 (28.7)
Education, y	18.0 (3.3)	18.1 (3.4)
MMSE score at baseline	28.3 (1.7)	28.5 (1.7)

Abbreviation: MMSE, Mini-Mental State Examination.

*Data are given as mean (SD) unless otherwise indicated.

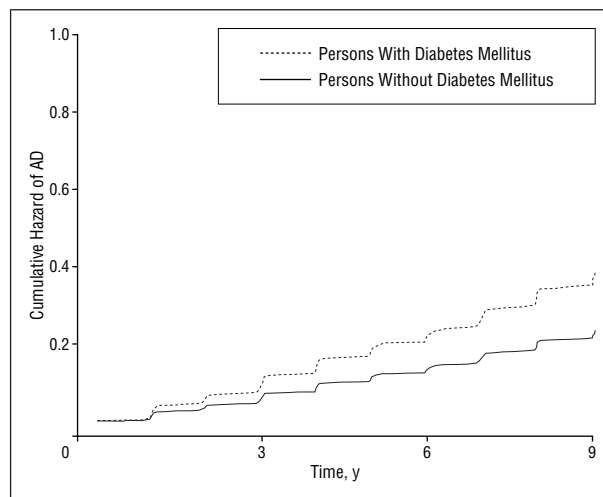


Figure 1. Cumulative hazard of Alzheimer disease (AD) among persons with diabetes mellitus compared with those without diabetes mellitus.

Persons with diabetes mellitus had lower baseline scores on measures of episodic memory, semantic memory, working memory, and visuospatial ability (**Table 2**). However, diabetes mellitus was only associated with a more rapid rate of decline in perceptual speed. In persons without diabetes mellitus, perceptual speed declined a mean of 0.08 unit per year (**Table 3**), whereas it declined an additional 0.03 unit per year in persons with diabetes mellitus, an increase of about 44%. This effect of diabetes mellitus on decline in perceptual speed, adjusted for age, sex, and educational level, is illustrated in **Figure 2**. Similar results were found in models with diabetes mellitus identified at baseline only (variable estimate for diabetes mellitus \times time for perceptual speed = -0.03 [$P = .08$] vs -0.03 [$P = .02$] when diabetes mellitus was defined based on all time points).

We conducted additional sets of analyses to evaluate whether stroke either confounded or modified the observed association of diabetes mellitus with decline in perceptual speed. Stroke slightly attenuated the relationship between diabetes mellitus and decline in perceptual speed (variable estimate for diabetes mellitus \times time for perceptual speed, controlling for stroke = -0.03 [$P = .05$]). There was an interaction between stroke and diabetes

Table 2. Baseline and Crude Change per Year in Cognitive Test Scores of Persons With and Without Diabetes Mellitus*

Cognitive System	Cognitive Test	Baseline		Crude Change/yr†	
		Persons With Diabetes Mellitus	Persons Without Diabetes Mellitus	Persons With Diabetes Mellitus	Persons Without Diabetes Mellitus
Episodic memory	Word List Memory	17.5 (3.5)	18.3 (4.1)	0 (1.8)	0.1 (1.6)
	Word List Recall	5.4 (1.8)	5.8 (2.1)	-0.1 (0.7)	0 (0.8)
	Word List Recognition	9.6 (0.8)	9.7 (0.8)	-0.1 (0.5)	-0.1 (0.5)
	Logical Memory Ia	11.6 (3.7)	12.1 (3.9)	0 (1.4)	0.2 (1.5)
	Logical Memory IIa	9.8 (4.4)	10.3 (4.2)	0.1 (1.4)	0.3 (1.3)
	Immediate story recall	9.5 (2.0)	9.7 (1.7)	-0.1 (0.8)	-0.1 (0.8)
Semantic memory	Delayed story recall	9.2 (2.0)	9.3 (2.0)	-0.2 (0.9)	-0.2 (1.0)
	Verbal Fluency	33.5 (9.8)	35.1 (8.8)	-1.0 (2.5)	-0.6 (2.7)
	Boston Naming Test	13.6 (1.3)	13.7 (1.4)	-0.1 (0.6)	-0.1 (0.5)
	Extended Range Vocabulary Test	10.3 (3.5)	10.7 (3.4)	-0.1 (1.0)	-0.2 (1.1)
Working memory	National Adult Reading Test	13.4 (3.8)	13.5 (4.2)	0.1 (0.9)	0.1 (1.0)
	Digit Span forward	7.9 (1.8)	8.4 (2.0)	-0.1 (0.6)	-0.1 (0.7)
	Digit Span backward	5.8 (1.8)	6.4 (2.1)	-0.1 (0.6)	0 (0.8)
	Digit ordering	6.8 (2.5)	7.0 (2.7)	-0.1 (0.8)	0 (0.8)
Visuospatial ability	Alpha span	5.0 (1.5)	5.1 (1.7)	-0.2 (0.5)	-0.1 (0.7)
	Judgment of Line Orientation	9.7 (3.4)	10.1 (3.1)	-0.2 (0.9)	-0.1 (1.1)
Perceptual speed	Standard Progressive Matrices	9.6 (3.3)	10.5 (3.4)	0 (1.0)	0 (1.2)
	Symbol Digit Modalities Test	39.5 (9.7)	40.4 (10.8)	-1.1 (3.7)	-0.8 (3.0)
	Number Comparison	25.6 (6.1)	25.4 (7.3)	-0.9 (2.6)	-0.4 (2.1)

*Data are given as mean (SD) test scores.

†The mean difference between scores from adjacent annual examinations.

Table 3. Random Effects Models Examining the Relation of Diabetes Mellitus to Baseline Level of and to Annual Rate of Change in Cognitive Function*

Cognitive System	Model Terms	Estimate	SE	P Value
Global cognitive function	Time	-0.03	0.01	<.001
	Diabetes mellitus	-0.16	0.04	<.001
	Diabetes mellitus × time	-0.02	0.01	.06
Episodic memory	Time	-0.03	0.01	.001
	Diabetes mellitus	-0.16	0.05	.003
	Diabetes mellitus × time	-0.02	0.02	.26
Semantic memory	Time	-0.05	0.01	<.001
	Diabetes mellitus	-0.14	0.06	.01
	Diabetes mellitus × time	-0.01	0.01	.43
Working memory	Time	-0.03	0.01	<.001
	Diabetes mellitus	-0.18	0.06	.001
	Diabetes mellitus × time	-0.01	0.01	.30
Visuospatial ability	Time	-0.02	0.01	<.001
	Diabetes mellitus	-0.21	0.06	.001
	Diabetes mellitus × time	-0.02	0.01	.08
Perceptual speed	Time	-0.08	0.01	<.001
	Diabetes mellitus	-0.08	0.07	.28
	Diabetes mellitus × time	-0.03	0.02	.02

*Analyses were adjusted for the effects of age, sex, educational level, and time interactions with age, sex, and educational level.

mellitus at baseline on level of perceptual speed (variable estimate = 0.35 [$P = .05$]), but there was no evidence that presence of stroke modified the impact of diabetes mellitus on rate of decline.

COMMENT

In a cohort of more than 800 older persons, we found that diabetes mellitus sometime in the study was associated with an increased risk of developing AD during a mean of 5.5 years of observation. The risk of incident AD was 65% higher in those with diabetes mellitus than in those without it.

Overall, results were similar in analyses restricted to diabetes mellitus identified at baseline only, although the confidence interval included 1. These results suggest that diabetes mellitus is related to risk of AD in old age.

These findings are consistent with the results of 2 large longitudinal cohort studies.^{5,6} In one study,⁵ diabetes mellitus doubled the risk of AD during 2 years of follow-up in a sample of more than 6000 older persons from a defined cohort. The other study,⁶ using data from about 2500 Japanese American men, found a similar result: diabetes mellitus approximately doubled the risk of AD. In contrast, 2 other longitudinal studies^{7,8} did not

demonstrate a significant association between diabetes mellitus and incident AD, but in both, the results were in the direction of increased risk.

Some,⁹⁻¹¹ but not all,¹² previous studies found that diabetes mellitus was related to change in cognitive function. One factor that may contribute to variability from study to study is that diabetes mellitus may be related to decline in some cognitive systems but not others. A novel feature of this study is that we assessed the relation of diabetes mellitus to decline in different domains of cognitive function that have previously been shown to be affected by some risk factors but not others.¹³⁻¹⁵ Although diabetes mellitus was related to level of global cognition and multiple cognitive domains at baseline, we found that diabetes mellitus was only related to decline in perceptual speed. The one study¹² that did not find a relation between diabetes mellitus and cognitive decline did not include a measure of perceptual speed.

Because diabetes mellitus is a chronic condition that is often present before a diagnosis is made or treatments are recommended, we used diabetes mellitus identified at any evaluation as the primary predictor. Furthermore, with more persons in the diabetes mellitus group, this approach increases the power to detect an association between diabetes mellitus and the outcome variables of interest. Indeed, the association of diabetes mellitus at baseline with incident AD did not reach significance, but the estimates were similar to those found in the analyses with diabetes mellitus identified at any evaluation.

The basis of the association between diabetes mellitus and AD is uncertain. Diabetes mellitus is a well-established risk factor for stroke. In a previous study,¹⁵ cerebral infarctions were preferentially associated with a measure of perceptual speed. This raises the possibility that cerebral infarctions mediate the association of diabetes mellitus with AD. Although we controlled for clinical evidence of stroke in the present analyses, the possibility that cerebral infarction accounts, in part, for the association of diabetes mellitus with clinical AD cannot be excluded, because many people with cerebral infarcts do not experience a clinical stroke.¹⁵ The partial attenuation of the effect of diabetes mellitus on decline in perceptual speed and the interaction between diabetes mellitus and stroke on level of perceptual speed also support the possibility that an infarction is likely to mediate some of the association between diabetes mellitus and AD. Large studies with pathological or brain imaging (eg, magnetic resonance imaging) data are needed to investigate this issue further.

Although diabetes mellitus is not known to be related to the pathological features of AD,²⁸ recent data raise the possibility of a more direct relation between diabetes mellitus and AD. For example, insulin has been reported to be related to memory function in patients with AD^{29,30} and to plasma amyloid level.³¹ In genetic linkage studies,^{32,33} a locus on chromosome 10 that is near the insulin-degrading enzyme gene has been linked to late-onset AD. In cell-culture experiments, the insulin-degrading enzyme has been shown to degrade amyloid β ,^{34,35} and, more recently, researchers³⁶ found that the insulin-degrading enzyme regulates amyloid β in vivo. Insulin has also been hypothesized to regulate τ phosphorylation.^{37,38} Finally,

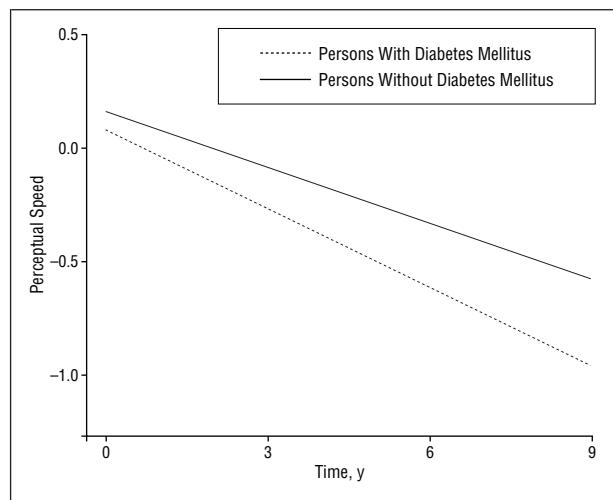


Figure 2. Predicted 9-year paths of change in perceptual speed in typical participants with and without diabetes mellitus.

other potential mechanisms include the production of advanced glycation end products³⁹ or alterations of oxidative stress pathways, calcium homeostasis, and hippocampal synaptic plasticity.⁴⁰ Further studies will be needed to investigate these and other possibilities.

The strengths of this study include the availability of a mean of 5.5 years of follow-up data with annual structured evaluations, which may have enhanced our ability to model change in cognitive function. Also, this longitudinal study benefits from a high follow-up rate, which minimizes selective attrition effects. Furthermore, we studied incident AD and change in cognitive function, using previously established composite measures of global cognitive function and 5 cognitive systems as independent outcomes. Finally, the homogeneity of the population may be considered a strength of the study, by controlling for the effects of potentially confounding variables, such as educational level, occupation, and lifestyle.

This study also has several limitations. Although the homogeneity of the study group may be a strength, it will be important to replicate our findings, particularly of the association of diabetes mellitus with change in cognitive function, in a diverse cohort that is more representative of the general population. Another limitation of our study concerns the identification of persons with diabetes mellitus. Diabetes mellitus was identified using medication data and/or self-report, but not serological data. However, analyses of data on inspection of all medications and on self-report suggested that self-report was a reliable means of assessing diabetes mellitus.

In summary, these findings suggest that diabetes mellitus is associated with AD and decline in cognitive function in older persons.

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and Bennett); *statistical expertise* (Dr Bienias); *obtained funding* (Drs Wilson, Evans, and Bennett); *administrative, technical, and material support* (Drs Arvanitakis, Wilson, Evans, and Bennett); *study supervision* (Drs Arvanitakis and Bennett).

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