

Diabetes Mellitus and Risk of Developing Alzheimer Disease

Results From the Framingham Study

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Background: Diabetes mellitus (DM) could increase the risk of Alzheimer disease (AD) through several biologically plausible pathways, but the relationship between DM and the development of AD remains uncertain.

Objective: To compare the risk of developing AD in subjects with and without DM.

Design: Prospective community-based cohort study.

Participants: Framingham Study Original cohort participants who were dementia free and attended the 16th biennial examination (n=2210 persons, 1325 women; mean age, 70 years).

Main Outcome Measures: Relative risk of incident AD (criteria from the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) associated with baseline DM (casual plasma glucose ≥ 200 mg/dL [≥ 11.1 mmol/L] or use of insulin or a hypoglycemic drug) in overall group and within subgroups defined by apolipoprotein E genotype and plasma homocysteine levels; mod-

els were adjusted for age, sex, and cardiovascular risk factors.

Results: At baseline, 202 participants (9.1%) had DM. During the follow-up period (mean, 12.7 years; range, 1-20 years), 17 of 202 persons with DM (8.4%) and 220 of 2008 persons without DM (11.0%) developed AD, yielding a relative risk of 1.15 (95% confidence interval, 0.65-2.05). Among subjects without an apolipoprotein E $\epsilon 4$ allele or elevated plasma homocysteine levels, 44 of 684 persons (6.4%) developed AD; relative risk for AD comparing diabetic patients with nondiabetic patients was 2.98 (95% confidence interval, 1.06-8.39; $P = .03$). The effect was strongest in persons aged 75 years or older with a relative risk of 4.77 (95% confidence interval, 1.28-17.72; $P = .02$).

Conclusion: Diabetes mellitus did not increase the risk of incident AD in the Framingham cohort overall; however, DM may be a risk factor for AD in the absence of other known major AD risk factors.

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DIABETES MELLITUS (DM) has been associated with cognitive decline,¹⁻⁸ anatomical measures of brain aging (whole-brain atrophy and hippocampal atrophy),⁹⁻¹¹ and with an increased risk of stroke and vascular dementia (VaD).¹²⁻¹⁶ The relationship between DM and Alzheimer disease (AD) is less clear; while some prior studies did find an association,^{1,17-20} others did not.^{13,14,21,22} The varying results may be due to differences in the age, ethnicity, sex, and risk factor profile of different study populations; variations in the study designs, criteria used to define DM, dementia, VaD, and AD; and varying lengths of follow-up. Prior studies relating DM to the risk of AD have either had a relatively short follow-up period of less than 6 years or substantial loss to follow-up.¹²

We had previously observed that the risk of developing dementia following stroke was greatest in younger, apolipo-

protein E (APOE) $\epsilon 4$ -negative participants, that is, in persons at the lowest a priori risk of developing dementia.²³ Furthermore, insulin resistance increased the risk of developing AD only among persons who were APOE $\epsilon 4$ negative.²⁴ We hypothesized that the association between DM and AD would also be best demonstrated in a long-term follow-up of subjects without other major known risk factors for AD (APOE $\epsilon 4$ genotype and an elevated plasma homocysteine [tHcy] level).

METHODS

Framingham Original cohort participants (n=2611) were enrolled in a dementia-free cohort between 1976 and 1978, based on their performance on a standardized neuropsychological test battery,²⁵ subsequent biennial Mini-Mental State Examinations,²⁶ and, in persons suspected to have cognitive impairment, fur-

Table 1. Characteristics of Study Sample at Baseline (16th Biennial) Examination*

Characteristic	Without Diabetes (n = 2008)	With Diabetes (n = 202)	P Value
Sex, % males	39	51	.002
Age, y	70.4 ± 6.9	71.5 ± 7.0	.045
Education, high school graduate, %	64	53	.002
Systolic blood pressure, mm Hg	139 ± 20	146 ± 19	<.001
Body mass index†	26.5 ± 4.3	28.5 ± 5.2	<.001
Apolipoprotein E genotype, %			
ε2/ε2 or ε2/ε3	11	9	.88
ε3/ε3	67	67	
ε2/ε4, ε3/ε4, or ε4/ε4	22	24	
Plasma homocysteine level, μmol/L	12.5 ± 7.5	12.2 ± 4.3	.42
Casual blood glucose level, mg/dL	89 ± 19	156 ± 89	<.001
Diabetes medications			
Insulin, %	0	18	<.001
Oral hypoglycemic, %	0	44	<.001
Alcohol			
0 drinks/d	38	52	
<2 drinks/d	44	35	<.001
≥2 drinks/d	18	14	
Current smoker, %	16	15	.70
Baseline cardiovascular disease			
Stroke, %	3	8	.002
Other cardiovascular disease, %	20	39	<.001

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.05551.

*Values are given as mean ± SD unless otherwise noted.

†Calculated as weight in kilograms divided by the square of height in meters.

ther evaluations by a neurologist. At the 16th biennial examination (1979-1982), 2210 participants (1325 women; mean age 70 ± 7.0 years) from this cohort remained free of dementia and attended the examination; they constituted our study sample. Informed consent was obtained from all participants using a consent form approved by the Institutional Review Board at the Boston University School of Medicine.

DIAGNOSIS OF INCIDENT DEMENTIA, AD, AND VaD

Methods used for dementia screening and follow-up have been previously described.^{27,28} Participants identified as demented met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria²⁹ and had definite dementia (Clinical Dementia Rating scale score ≥1)³⁰ for a period of 6 months or longer. Participants diagnosed with AD met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for definite or probable AD,³¹ while those with VaD met Alzheimer Disease Diagnostic and Treatment Center criteria for probable VaD.³² Persons with more than 1 possible cause for their dementia were included only in the all-dementia analysis.

DIAGNOSIS OF DM

We defined DM as the documented use of insulin or an oral hypoglycemic drug or a casual (nonfasting) plasma glucose level greater than or equal to 200 mg/dL (11.1 mmol/L), recorded at the 16th biennial examination or at an earlier examination.³³

DEFINITION OF COVARIATES

The APOE genotype data were available for only 1139 persons (51%), as other participants either died before DNA could be collected for genotyping, or they refused consent.³⁴ Participants were dichotomized into those with and those without an APOE ε4 allele. Information on all other covariates—plasma tHcy levels (dichotomized as within or below the top age and sex quartile), educational status (dichotomized at high school completion), current cigarette smoking, alcohol intake (0, <2, or ≥2 drinks per day), systolic blood pressure, body mass index, baseline cardiovascular disease, and stroke—was available for most participants.

STATISTICAL ANALYSIS

In our primary analysis, the exposure variable was the presence or absence of DM at the 16th biennial examination, which we related to the subsequent development of all-cause dementia, AD, and VaD (until December 2003) using Cox proportional hazards regression models (age- and sex-adjusted, and multivariable models). Alzheimer disease and VaD were treated as competing risks. In subjects for whom APOE genotype data were available, we further adjusted for APOE ε4 status. We examined effect modification by age, sex, baseline blood pressure, diabetes treatment, a priori risk status, and availability of APOE ε4 genotyping by incorporating corresponding interaction terms in the analyses. We further estimated the risks of developing all dementia and AD within subgroups of subjects at a lower a priori risk of developing dementia and AD. In secondary analyses we modeled diabetes as a time-dependent covariate. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS

At baseline, 202 (9.1%) of the 2210 study participants had DM; 98 subjects (4.4%) had a documented blood glucose level greater than 198 mg/dL (11 mmol/L), and 176 subjects (8%) were receiving insulin or oral hypoglycemic drugs. Demographic and baseline characteristics of the diabetic and nondiabetic subjects are compared in **Table 1**.

During a 20-year follow-up period (range, 1-20 years; mean, 12.7 years), 319 of the 2210 participants became demented (237 had definite or probable AD; 32 had probable VaD). Low-risk subjects who did not have either a plasma tHcy level in the top quartile or an APOE ε4 gene had a relative risk (RR) for AD of 0.32 (95% confidence interval, 0.23-0.47; $P < .001$), and very low-risk subjects with these traits who were also aged less than 75 years had a RR for AD of 0.24 (95% confidence interval, 0.15-0.39; $P < .001$), compared with all subjects.

Using either the standard or the time-dependent Cox models, we found that overall, DM did not increase the risk of all-cause dementia and AD, but in the standard Cox models, there was an increased risk in the subgroup of low-risk and very low-risk subjects (**Table 2**). This difference in risk was seen throughout the period of follow-up (**Figure 1** and **Figure 2**). We found effect modification by age (higher risk in younger subjects; $P < .05$) and a priori risk status, but did not find effect modification by sex, diabetes treatment, baseline blood pressure, or availability of APOE genotyping.

Table 2. Multivariable Cox Proportional Hazards Models Examining the Relation Between Diabetes and the Risk of All-Cause Dementia, Alzheimer Disease, and Vascular Dementia Using Standard and Time-Dependent Cox Models

Variables Adjusted for in Multivariable Analysis	All-Cause Dementia		Alzheimer Disease		Vascular Dementia	
	Cases/N	HR (95% CI)	Cases/N	HR (95% CI)	Cases/N	HR (95% CI)
All cases						
Age, sex	319/2210	1.19 (0.79-1.78)	237/2210	1.07 (0.65-1.75)	32/2210	1.81 (0.63-5.23)
Multivariable*	233/1594	1.20 (0.74-1.96)	176/1594	1.15 (0.65-2.05)	23/1594	0.81 (0.18-3.70)
Age <75 y, multivariable*	122/1183	1.99 (1.04-3.7)	82/1183	1.21 (0.99-4.96)	17/1183	1.21 (0.23-6.37)
		(<i>P</i> = .04)				
Time-dependent, multivariable*	233/1594	1.14 (0.61-2.11)	176/1594	1.35 (0.68-2.70)	23/1594	1.60 (0.34-7.62)
Subjects with APOE ε4 information						
Age y, sex	186/1290	1.18 (0.64-2.18)	140/1290	1.02 (0.48-2.19)	18/1290	3.54 (1.01-12.44)
						(<i>P</i> = .049)
Multivariable*	142/1009	1.40 (0.70-2.81)	107/1009	1.44 (0.66-3.18)	13/1009	1.24 (0.15-10.11)
Multivariable* + APOE ε4	142/1009	1.20 (0.60-2.40)	107/1009	1.14 (0.52-2.51)	13/1009	1.24 (0.15-10.11)
Age <75 y, multivariable*	86/853	22.20 (0.94-5.18)	58/853	2.39 (0.84-6.81)	12/853	1.74 (0.21-14.55)
Time-dependent, multivariable* + APOE ε4	142/1009	1.58 (0.78-3.20)	107/1009	1.88 (0.84-4.19)	13/1009	2.93 (0.54-15.75)
Subjects with plasma homocysteine in lower 3 quartiles and without APOE ε4						
Age, sex	65/684	2.48 (1.10-5.60)	44/684	2.91 (1.10-7.71)	9/684	1.80 (0.21-15.27)
		(<i>P</i> = .03)		(<i>P</i> = .03)		
Multivariable*	58/607	2.39 (0.96-5.91)	39/607	2.98 (1.06-8.39)	7/607	
				(<i>P</i> = .04)		
Time-dependent, multivariable*	58/607	1.88 (0.93-3.80)	39/607	2.24 (0.97-5.21)		
Subjects <75 y with plasma homocysteine in lower 3 quartiles and without APOE ε4						
Age, sex	37/591	3.37 (1.30-8.73)	21/591	3.94 (1.15-13.54)	8/591	2.28 (0.27-19.28)
		(<i>P</i> = .01)		(<i>P</i> = .03)		
Multivariable*	32/517	3.54 (1.17-10.770)	18/517	4.77 (1.28-17.72)	6/517	
		(<i>P</i> = .03)		(<i>P</i> = .02)		
Time-dependent, multivariable*	32/517	2.13 (0.85-5.30)	18/517	2.46 (0.73-8.21)		

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio.

*Adjusted for age, sex, education, plasma homocysteine, systolic blood pressure, body mass index, current smoking, alcohol use, prevalent stroke, and cardiovascular disease.

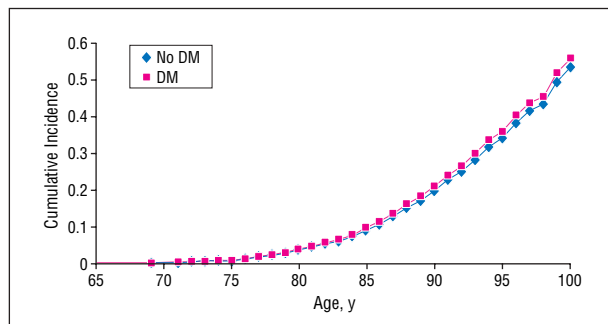


Figure 1. Cumulative incidence of Alzheimer disease in entire sample: comparison of groups with and without diabetes mellitus (DM), adjusted for age and sex.

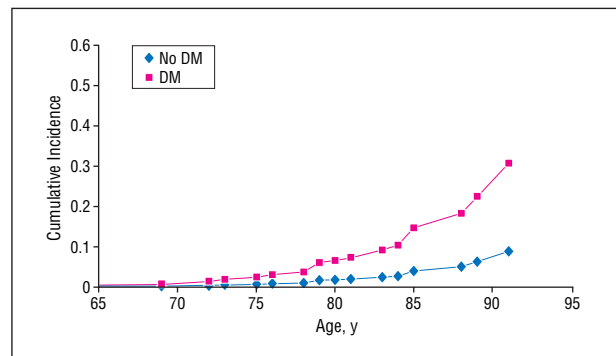


Figure 2. Cumulative incidence of Alzheimer disease in low-risk group: comparison of persons with and without diabetes mellitus (DM), adjusted for age and sex.

Our numbers are too small to permit a definitive conclusion regarding the risk of developing VaD.

COMMENT

Diabetes mellitus was not an independent risk factor for AD in the overall Framingham Study sample, but it was a strong independent risk factor for AD among persons at a relatively lower initial risk for developing the disease (those who were APOE ε4 negative and did not have a plasma tHcy level in the highest age- and sex-specific

quartile), raising the RR for AD by 3- to 5- fold in this group. The RR was greatest in younger subjects (<75 years of age) in whom the population-attributable risk from DM was 25%. Our findings suggest that an influence of DM on AD risk may be evident in subgroups of study populations in which there is no evidence for an overall association between these traits.

The strengths of our study are its community-based sample, prospective study design, and the direct ascertainment of exposure and outcome status. Selection bias was minimized by population enrollment well before the

onset of diabetes or dementia, and intensive, ongoing follow-up of survival and cognitive status. The ongoing determination of diabetic status at each biennial examination, starting well before the onset of dementia, minimized the possibility of an ascertainment bias. Finally, subjects were observed for up to 2 decades.

An important limitation is the predominantly white study population. Further, we used casual (nonfasting) rather than fasting blood glucose levels and hence, we may have misclassified patients with impaired glucose tolerance as nondiabetic, which would bias the results of our overall and subgroup analyses toward the null hypothesis, but would not explain our findings of increased risk in some subgroups.

Our findings are consistent with the results of several prior studies,^{13,14,17,21,22} which either did not show an association between DM and the subsequent risk of developing AD or described such an association only in specific subgroups (men, persons with systolic blood pressure >180 mm Hg, or APOE ε4 genotype positive).^{13,17,19} They differ from the findings of a few large population-based studies that did report an overall association.^{1,18,20,35} One possible explanation for this discrepancy is variation in the definition and prevalence of DM between the studies.

We found that the RR of developing AD attributable to DM was highest in subjects without the 3 known AD risk factors: a tHcy level in the top quartile, an APOE ε4 gene, or age 75 years or older. No prior studies have addressed the risk in this specific subgroup, but a higher RR of AD associated with DM has been described in subjects younger than 75 years compared with subjects older than 85 years.¹⁸ The Kungsholmen project¹³ reported no interaction between DM and the APOE ε4 genotype, while the Honolulu-Asia Aging study¹⁹ observed a higher RR among diabetic patients with an APOE ε4 genotype. These differences could be due to chance or differences in ethnicity and sex distribution in the populations. Prior studies have suggested that the brains of AD subjects without an APOE ε4 gene may be more susceptible to the adverse effects of hyperinsulinemia; this provides a possible biological rationale for our epidemiological findings.³⁶

There are several biologically plausible, nonvascular pathways that could mediate an association between DM and AD. Diabetes mellitus promotes the formation of advanced glycation end products,³⁷ inflammation,³⁸ and neurofibrillary tangle formations.³⁹ Insulin resistance and the resulting hyperinsulinemia appear to increase the risk of AD.⁴⁰ Finally, common genetic pathways may underlie the development of both DM and AD; as one example, mutations in the insulin-degrading enzyme that induce DM⁴¹ also impair the degradation of β-amyloid protein.⁴²

Our findings emphasize the need to consider DM as a potential risk factor for cognitive impairment, dementia, and AD. The utility of cognitive testing and improved diabetic control in reducing the risk of AD in persons with diabetes need to be addressed in further studies.

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