



Risk of Alzheimer's Disease in People with Diabetes Mellitus

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ABSTRACT

Background: Diabetes Mellitus (DM) may increase the risk of Alzheimer's disease (AD) in a number of biologically conceivable ways, although how DM and the development of AD are related is still unclear.

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

Design: Prospective community-based cohort study.

Participants: Framingham Research Participants (n=2210; 1325 women; mean age, 70 years) who were part of the first cohort, did not have dementia and did not participate in the biennial test.

Results: Relative risk of incident Alzheimer's disease within the overall group and within subgroups defined by plasma homocysteine levels and apolipoprotein E genotype (based on criteria from the National Institute of Neurological and Communicative Diseases and Stroke/Association for Alzheimer's Disease and Related Disorders); models were adjusted for age, sex, and cardiovascular risk factors. At baseline, 202 people (9.1%) had DM. During the follow-up period (mean, 12.7 years; range, 1-20 years), the risk of developing AD was 1.15 (95% confidence interval, 0.65-2.05) in 17 of 202 people with diabetes (8.1%) and 220 of 2008 people without diabetes (11.0%). Among the 684 participants, 44 (6.4%) did not have elevated plasma homocysteine levels or an apolipoprotein E4 allele; the relative risk of AD was 2.98 (95% confidence interval, 1.06-8.39; P=.03) in patients with diabetes compared to those without diabetes. The effect was greatest among individuals 75 years of age or older, with a relative risk of 4.77 (95% confidence interval, 1.28-17.72; P=.02).

Conclusion: Overall, Diabetes Mellitus did not increase the incidence of incident AD in the Framingham cohort; however, in the absence of other major risk factors for AD, Diabetes Mellitus may be a risk factor for AD.

Keywords: Diabetes Mellitus (DM); Alzheimer Disease (AD); Brain; Ageing

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INTRODUCTION

Diabetes Mellitus (DM) has been associated with morphological measures of brain ageing, hippocampus and whole-brain shrinkage, cognitive impairment, an increased risk of stroke, and Vascular Dementia (VaD). It is unclear how DM and Alzheimer Disease (AD) are related; some previous research has detected a link, but others have not. These various results could be a result of differences in age, ethnicity, sex, and risk factor profiles; study designs; definitions of DM, dementia, VaD, and AD; and follow-up periods. In earlier studies linking DM to the risk of AD, the follow-up time was either quite brief (less than 6 years) or large. We previously noted that younger, *APOE4* negative participants—those with the lowest a priori risk of developing dementia—had the highest probability of developing dementia after stroke. Furthermore, only those people who lacked *APOE4* had a greater chance of developing AD due to insulin resistance. We therefore reasoned that the best way to show the connection between DM and AD would be to perform a long-term follow-up of participants who did not have the two primary recognized risk factors for AD (elevated plasma homocysteine (tHcy) level and the *APOE4* genotype).

MATERIALS AND METHODS

Birmingham the original cohort participants (n=2611) were enrolled in a dementia-free cohort between 2000 and 2022 based on their data from a standard battery of neuropsychological tests and subsequent biennial Mini-Mental State Testing and, in the case of individuals suspected of having cognitive problems, further evaluations by a neurologist. Our study sample consisted of 2210 patients (1325 women; mean age 70 years) from this cohort who were still free of dementia at the biannual examination (2000-2022). Informed consent was obtained from each participant after providing consent from the Institutional Review Board [1-3].

Diagnosis of incident dementia, AD, and VaD

Previous descriptions of dementia screening and follow-up procedures have been made. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria were met by the participants who were classified as having dementia. Additionally, they had a clinically evident case of dementia (a score of 1 on the CDR scale) for a minimum of six months [4]. Participants with ADs met the criteria for definite or probable ADs set forth by the Alzheimer Disease Diagnostic and Treatment Centre, while those with VaD met the criteria for probable VaD established by the National Institute of Neurological and Communicative Diseases and Stroke. Only 32 individuals with multiple dementia-related causes were included in the study of all dementias.

Diagnosis of DM

DM was defined as follows: A documented history of using insulin, oral hypoglycemic medication, or a casual (nonfasting) plasma glucose level of more than or equal to 200 mg/dL (11.1

mol/L), as measured at the biannual assessment or at an earlier examination.

Definition of variables

Only 1139 people (51%) had available *APOE* genetic information since the remaining participants either passed away before they could decline to provide consent or had their DNA taken for genotyping. Two groups of participants were created: Those who lacked the *APOE4* allele and those who did. The majority of participants were able to view information on all other covariates, such as systolic blood pressure, body mass index, baseline cardiovascular disease, stroke, current cigarette smoking, alcohol intake (0, <2 or >2 drinks per day), educational level (dichotomized at high school graduation), and plasma tHcy levels (dichotomized as within or below the top age and sex quartile).

Statistical analysis

The presence or absence of DM at the biennial assessment served as the exposure variable, and we used Cox proportional hazards regression models (age and sex-adjusted, multivariable models) to relate the presence or absence of DM to the development of all-cause dementia, AD, and VaD (until December 2033). VaD and Alzheimer's disease are viewed as conflicting hazards. We further corrected for *APOE4* status in participants for whom *APOE* genotype data were available. By integrating the relevant interaction terms into the analysis, we examined how age, sex, baseline blood pressure, diabetes treatment, a priori risk status, and the accessibility of the *APOE4* genotype affected the effect modification. We assessed the chances of having dementia and AD in subgroups of people who were a priori less likely to develop dementia and AD. Diabetes was modeled as a time-dependent covariate for secondary analysis. SAS software was used for all the statistical analyses.

RESULTS

At baseline, of the 2210 trial participants, 202 (9.1%) had diabetes at the beginning of the study, 98 (4.4%) had a confirmed blood glucose level higher than 198 mg/dL (11 mmol/L), and 176 (8%) were using insulin or an oral hypoglycemic medication. Table 1 compares the demographic and baseline characteristics of the participants with and without diabetes. A total of 319 of the 2210 patients developed dementia throughout the course of the 20-year follow-up period (range, 1-20 years; mean, 12.7 years; 237 had definite or probable AD; 32 had probable VaD). In comparison to all the subjects, the Relative Risk (RR) for Alzheimer's Disease (AD) was 0.32 (95% confidence interval, 0.23-0.47; P<.001) for low-risk individuals without the *APOE4* gene or a plasma tHcy level in the top quartile and 0.24 (95% confidence interval, 0.15-0.39; P<.001) for very low-risk individuals who were also under 75 years old. Using both conventional and time-dependent Cox models, we discovered that, generally, DM did not increase the risk of AD or all-cause dementia; however, the subgroup of participants

who were considered low risk and very low risk according to the standard Cox models did have an increased risk. Throughout the follow-up period, this difference in risk persisted (Figures 1 and 2). Age and a priori risk status were found to be effect

modifiers (greater risk in younger patients; P.05); in contrast, APOE genotyping availability, baseline blood pressure, diabetes therapy, and sex were not. We do not have enough data to draw any firm conclusions on the likelihood of developing VaD.

Characteristics of study sample at baseline (16 th Biennial) Examination*			
Characteristic	Without diabetes (n=2008)	With diabetes (n=202)	P-value
Sex, % males	39	51	0.002
Age, yr	70.4 ± 6.9	71.5 ± 7.0	0.045
Education, high school graduate,%	64	53	0.002
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, %			
Δ2/ε2 or ε2/ε3	11	9	0.88
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	0.42
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	0.7
Baseline cardiovascular disease			
Stroke, %	3	8	0.002
Other cardiovascular disease, %	20	39	<.001

Table 1: SI conversion factors-To convert glucose to millimoles per liter, multiply by 0.05551. **Note:** *: Values are given as the mean ± SD unless otherwise noted, †: Calculated as weight in kilograms divided by the square of height in meters.

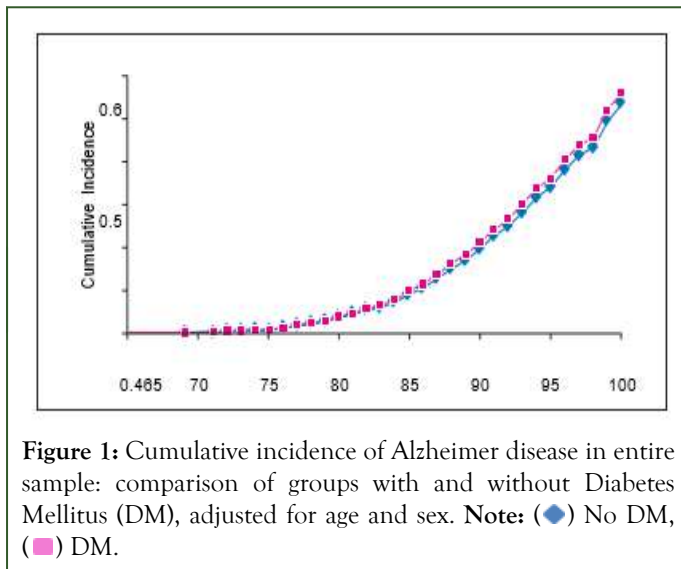


Figure 1: Cumulative incidence of Alzheimer disease in entire sample: comparison of groups with and without Diabetes Mellitus (DM), adjusted for age and sex. **Note:** (◆) No DM, (■) DM.

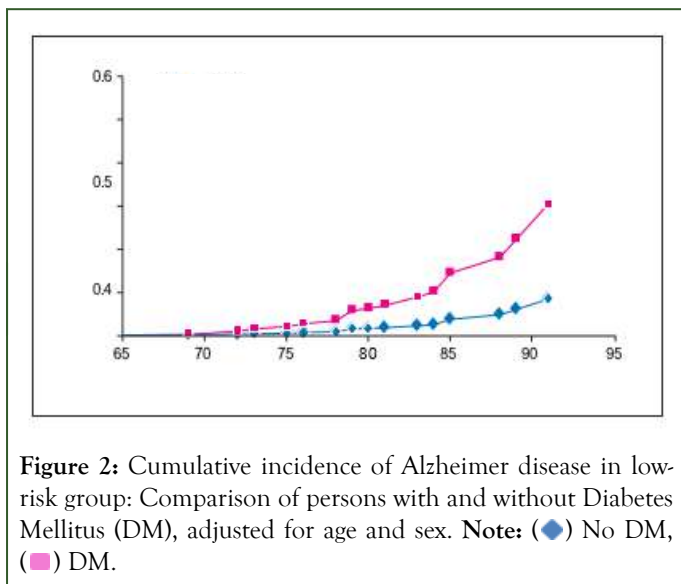


Figure 2: Cumulative incidence of Alzheimer disease in low-risk group: Comparison of persons with and without Diabetes Mellitus (DM), adjusted for age and sex. **Note:** (◆) No DM, (■) DM.

DISCUSSION

According to the entire Framingham Study sample, Diabetes Mellitus increased the risk of AD by three to five times in patients who had a relatively lower initial risk of the disease (those who were *APOE4* negative and did not have plasma tHcy levels in the highest age and sex-specific quartile). However, Diabetes Mellitus was not an independent risk factor for AD. The population-attributable risk factor for DM was 25% in younger patients (<75 years of age), where the RR was highest. Our results imply that DM may affect AD risk in study population subpopulations in which there is no proof of an overall relationship between these features [5]. The strengths of our investigation include its prospective study design, direct confirmation of exposure and outcome status, and community-based population. By enrolling the population well in advance of diabetes or dementia development and by closely monitoring survival and cognitive health throughout time, selection bias was reduced. The likelihood of an ascertainment bias was reduced by the continual determination of diabetes status at each biennial examination, beginning long before the development of

dementia. Finally, subjects underwent up to one year of observation [6-8]. The study population's predominance of white people is a significant restriction. Additionally, because we used casual (nonfasting) blood glucose levels rather than fasting blood glucose levels, we might have mistakenly classified patients with impaired glucose tolerance as nondiabetic patients. The null hypothesis would benefit from this bias in the overall and subgroup analyses, but it would not explain our observations of higher risk in certain subgroups [9-11]. Our results are consistent with a number of previous and, which neither did not show a link between DM and the risk of developing AD nor did they only occur in certain subgroups (men, people whose systolic blood pressure was less than 180 mm Hg, or people who had the *APOE4* genotype), and These findings are not consistent with the results of a few sizable population-based studies that did establish a general association [12]. The prevalence and definition of Diabetes Mellitus (DM) varied among the studies, which may be one explanation for this discrepancy. We discovered that participants lacking the three established AD risk factors-those with a tHcy level in the top quartile, an *APOE4* gene, or age 75 or older-had the highest probability of developing AD, which may be attributed to DM. The risk in this particular category has not been studied previously; however, subjects younger than 75 years of age have been shown to have a higher risk of AD associated with DM than subjects older than 85 years [13-16]. The Kungsholmen project revealed no correlation between the *APOE4* genotype and diabetes incidence, despite the findings of the Honolulu-Asia Aging study revealing a greater RR among patients with this genotype. These discrepancies may be the result of chance, racial, or sex disparities in the population or both. Our epidemiological findings may have a biological basis; as prior research has revealed that AD patients lacking the *APOE4* gene may be more vulnerable to the harmful consequences of hyperinsulinemia. Numerous biologically conceivable, nonvascular mechanisms could be used to mediate the link between DM and AD. Advanced glycation end products, inflammation, and neurofibrillary tangle development are all encouraged by Diabetes Mellitus [17,18]. The risk of AD appears to be increased by insulin resistance and subsequent hyperinsulinemia. Similar genetic mechanisms may play a role in the development of AD and DM. For example, mutations in the insulin-degrading enzyme that result in DM41 also impact the degradation of amyloid protein [19,20].

CONCLUSION

Our findings demonstrate the importance of considering DM a potential risk factor for AD, dementia, and cognitive decline. Diabetes Mellitus did not increase the incidence of incident AD in the Framingham cohort; however, in the absence of other major risk factors for AD, Diabetes Mellitus may be a risk factor for AD. The usefulness of cognitive testing and scientifically validated diabetic control in reducing the risk of AD in individuals with diabetes needs to be investigated further.

Conflicts of interest

None

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