Diabetes mellitus and risk of dementia in the Kungsholmen project: A 6-year follow-up study

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Abstract—*Background:* Research on diabetes mellitus as a risk factor for dementia and its main subtypes has produced conflicting results. The authors investigated the relationship between diabetes mellitus and risk of dementia, Alzheimer disease (AD), and vascular dementia (VaD). *Methods:* A dementia-free cohort of 1,301 community dwellers aged 75 years and older in Stockholm, Sweden, was longitudinally examined twice over 6 years to detect dementia cases (Diagnostic and Statistical Manual of Mental Disorders–III-R diagnostic criteria). Cox proportional hazards models were used to analyze the data with adjustment for several potential confounders. *Results:* During the 5,584 person-years of follow-up, 350 subjects developed dementia, including 260 AD and 49 VaD cases. Diabetes mellitus was associated with hazard ratios (HR) of 1.5 (95% CI 1.0 to 2.1, $p = 0.04$) for dementia, 2.6 (95% CI 1.2 to 6.1) for VaD, and 1.3 (95% CI 0.9 to 2.1) for AD. Patients who were treated with oral antidiabetic medications had HRs of 1.7 (95% CI 1.0 to 2.8, $p = 0.04$) for dementia and 3.6 (95% CI 1.3 to 9.5) for VaD. There were significant interactions of diabetes with severe systolic hypertension (≥180 mm Hg) on dementia and its main subtypes, and of diabetes with heart disease on VaD. *Conclusions:* Diabetes mellitus increases the risk of dementia, and VaD in particular, in very old people. The risk for dementia and VaD is especially high when diabetes mellitus occurs together with severe systolic hypertension or heart disease.

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Dementia and diabetes mellitus are both highly prevalent disorders among the elderly.[1,2] Cross-sectional[3,4] and prospective[5-7] studies provide substantial evidence that diabetes is associated with cognitive impairment involving both memory and executive functions. With regard to dementia, some diabetic complications and comorbidities are implicated as risk factors for dementia and Alzheimer disease (AD). In addition, an association between diabetes and increased risk of dementia has been found in both cross-sectional[8-10] and prospective studies.[11-13] It remains unclear whether the risk effect of diabetes is specific to AD or vascular dementia (VaD). A number of cross-sectional studies indicate that diabetes mellitus is associated with dementia and VaD,[10,14] but not with AD.[15,16] An autopsy study found no significant difference in Alzheimer-type pathology between diabetic and nondiabetic subjects.[17] Longitudinal data from the Rotterdam study show that diabetes is associated with an increased risk of AD, especially for subjects with insulin treatment.[12] Several other longitudinal studies also reveal that diabetes increases the risk of AD.[11,13,18] By contrast, a population-based prospective study in Sweden and the Canadian Study of Health and Aging (CSHA) demonstrate that diabetes is associated with VaD independent of other vascular diseases, but not with AD.[19,20]

Diabetes mellitus is a major risk factor for cerebrovascular disease, a disorder that significantly increases the risk of dementia.[21] It is likely that a part of the association between diabetes and dementia is mediated by cerebrovascular disease. A multiethnic community cohort study found that diabetes increased the risk of stroke-related dementia.[22] However, other cross-sectional and longitudinal studies also show that the associations between diabetes and cognitive impairment and dementia persist even after adjusting for stroke.[3,8] Several studies concerning the role of diabetes in poststroke dementia have produced conflicting results.[23] In addition, few studies indicate that *APOE*-ϵ4 allele may interact with diabetes to affect the development of cognitive impairment and dementia.[13,24]

Cross-sectional data from a random sample within the Kungsholmen project show that diabetes is related to cognitive impairment.[25,26] Using the 6-year follow-up data from the same project, the present study aims to investigate the association between diabetes and risk of dementia, to examine whether diabetes is differentially related to subtypes of dementia, and to explore whether the diabetes-dementia association is mediated through vascular

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factors. In addition, the joint effects of diabetes and hypertension, heart disease, stroke, or *APOE*-ϵ4 allele on dementia were also assessed.

Methods. *Study population.* The Kungsholmen Project is a community-based, longitudinal study on aging and dementia as described in detail elsewhere.[27,28] In brief, the initial population of the project covered all registered inhabitants who were 75 years and older in October 1987 and were living in the Kungsholmen district of Stockholm, Sweden. By a two-phase design, 1,473 of the 1,810 baseline participants were diagnosed as being free of dementia (1987 to 1989). Of them, 172 subjects refused to participate in the first follow-up examination (1991 to 1993) or had moved before the examination. Therefore, the study population for the current analysis consisted of 1,301 baseline non-demented subjects. Of these individuals, 987 received a full dementia workup at first follow-up, which included a structured interview by nurses, a comprehensive clinical examination by physicians, and neuropsychological assessments by psychologists. Among the 788 subjects who remained free of dementia at first follow-up, 44 refused to undertake the second follow-up examination (1994 to 1996), and 568 persons underwent the examination following the same procedure as used at first follow-up. Medical records and death certificates were available for all individuals who died during the first (n = 314) or second (n = 176) follow-up period. The Ethics Committee of the Karolinska Institutet approved all phases of the project.

Baseline data collection. Information on medical history at baseline was derived from the computerized inpatient register system, which encompassed all hospitals in Stockholm since 1969. The International Classification of Diseases, eighth revision (ICD-8) was used to define the diseases and medical conditions in this register system. Data on medical drug use were collected for the 2 weeks preceding the baseline survey. Both prescription and non-prescription drug use were inquired about, and if possible, the drug containers and prescriptions were inspected to verify this information. Drug use was coded and classified according to the Anatomic Therapeutic Chemical (ATC) classification system.[29] Blood samples were taken at baseline, and blood glucose level was measured using a glucose oxidase procedure.[26] Data on blood glucose were available for 95.9% (n = 1,248) of the subjects. Diabetes mellitus at baseline was considered to be present if the subject was registered with diabetes (ICD-8 code 250), or the subject was taking antidiabetic drugs (hypoglycemic medications or insulin injection, ATC code A10), or the blood glucose level was higher than 11 mmol/L.[30]

Data on demographics (age, sex, and education) were collected from the subjects at baseline interview according to standardized protocols.[27,28] Educational levels were measured by the maximum years of formal schooling and dichotomized into <8 years and ≥ 8 years according to a previous study.[31] Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Arterial blood pressure was measured by trained nurses with sphygmomanometer. Blood pressure reading at baseline was missing for 31 persons. Genomic DNA was extracted from peripheral blood samples that were taken at baseline, and a standard PCR was used for *APOE* genotyping.[32] Data on *APOE* genotype were available for 75.7% (n = 985) of the study participants.

Other vascular disorders at baseline were identified through the impatient register system, which included heart disease (ICD-8 codes 410 to 414, 427, and 428) and stroke (ICD-8 codes 430 to 438). Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (ATC codes C02, C03, and C07).

Diagnosis of dementia, AD, and vascular dementia. The incident cases were all subjects who developed dementia over the two follow-up periods. The Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM-III-R) criteria[33] were used to define dementia with a three-step diagnostic procedure, i.e., two examining physicians independently made a preliminary diagnosis and a third opinion was asked for in case of disagreement.[34] The cases fulfilling the DSM-III-R criteria were denominated "clinically definite dementia," in contrast with a category of "questionable dementia," which was used when there was evident memory impairment but dysfunction of a second cognitive ability was questionable. In this analysis, we treated both groups as dementia. The diagnosis of AD required gradual onset, progressive deterioration, and lack of any other specific causes of dementia. The diagnosis of VaD required abrupt onset, stepwise deterioration, history of stroke, or focal deficits. Hachinski's ischemic scale[35] was used to support the differential diagnosis between AD and VaD. The diagnosis of dementia subtype was made clinically, without using the neuroimaging or pathologic data. Our diagnostic criteria for AD and VaD were equivalent to probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[36] and to possible VaD according to National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria.[37] For the deceased subjects, the diagnosis of dementia and subtypes was made by two physicians through reviewing the medical records and death certificates. Details of the clinical examination and diagnostic procedure have already been reported elsewhere.[28]

Data analyses. The statistical differences were examined with *t*-test for means and chi-square test for proportions. The incidence rate was calculated as the number of events divided by person-years of follow-up.[28] Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% CI of dementia, AD, and VaD diagnosed during the two follow-up periods in relation to diabetes and blood glucose level determined at baseline. Similar analyses were conducted separately for the use of antidiabetic medications. The joint effect between two factors (e.g., factors A and B) was assessed by dividing subjects into four categories of those with neither of them (reference), with A but without B, without A but with B, and with both A and B. The statistical interaction was examined by including the two independent variables and their cross-product term in the same model. We considered age (in years), sex, education, stroke, heart disease, BMI (in kg/m^2), systolic pressure (in mm Hg), diastolic pressure (in mm Hg), and antihypertensive drug use as covariates in all multivariate analyses. *APOE* genotypes were grouped as having any ϵ4 allele vs no ϵ4 allele. All types of dementia combined, AD, and VaD were used as separate outcomes in all Cox regression analyses.

Results. At baseline, 114 (8.8%) of the 1,301 participants were identified as having diabetes mellitus. Of them, 42 (36.8%) used oral medications, and 6 (5.3%) were treated with insulin.

During the 5,584 person-years of follow-up (median, 4.7; range, 0.01 to 8.3 years; the minimum follow-up period was due to death), 350 subjects developed dementia, including 260 AD (74.3%) and 49 VaD (14.0%) cases. Table 1 shows the baseline characteristics of the study population by diabetes status. There was no significant difference in the distribution of age, sex, *APOE*-ϵ4 allele, or stroke between the two groups. However, a higher proportion of a lower level of education, use of antihypertensive drugs, and heart disease was seen among diabetic individuals than those without the disease. The relation of diabetes mellitus to high BMI, high systolic pressure, and low diastolic pressure was significant or marginally significant.

Diabetes mellitus and all types of dementia, AD, and VaD. As shown in table 2, diabetes mellitus was significantly related to an increased risk for all dementias and VaD, even when a number of potential confounders including some vascular disorders were taken into account. In a separate analysis, diabetic patients who used oral antidiabetic medications were at substantial risk for all dementias and VaD. The relation of insulin treatment to dementia was not separately analyzed, because very few subjects were treated with insulin in our population (n = 6, two dementia cases).

A higher blood glucose level (>11 mmol/L) was specifically related to an increased risk of VaD. When the blood glucose level was entered as a continuous variable, the

Table 1 *Baseline characteristics of the initial dementia-free cohort of the Kungsholmen Project by diabetes mellitus status (n = 1,301)*

Characteristic	Diabetes mellitus		*p* Value
	No, n = 1,187	Yes, n = 114	
Age, y, mean (SD)	81.5 (5.0)	81.4 (4.8)	0.94
Female sex, %	75.1	74.6	0.91
Educational level ≥8 years, %	42.0	33.3	0.07
Body mass index, kg/m^2, mean (SD)	23.5 (3.6)	24.1 (3.4)	0.06
Any *APOE*-ϵ4 allele,* %	22.2	15.8	0.28
SBP,† mm Hg, mean (SD)	155.1 (21.4)	159.5 (24.2)	0.04
DBP,† mm Hg, mean (SD)	81.2 (10.9)	79.1 (9.6)	0.05
Antihypertensive drug use, %	43.2	64.0	<0.001
Stroke, %	6.7	10.5	0.13
Heart disease, %	14.5	29.8	<0.001

* Data on *APOE* genotypes were missing for 316 subjects, including 25.6% of subjects with diabetes mellitus and 24.2% of those without the disease.

† Information on blood pressure was missing for 31 subjects, including 3.5% of subjects with diabetes mellitus and 2.3% without the disease.

SBP = systolic blood pressure; DBP = diastolic BP.

adjusted HR per 1-mmol/L increment was 1.3 (95% CI 1.1 to 1.5) for VaD.

Combined effect of diabetes with severe systolic hypertension, heart disease, or APOE-ϵ4. Table 3 shows the combined effect of diabetes with either severe systolic hypertension (≥180 mm Hg) or heart disease or *APOE*-ϵ4. Diabetes mellitus in combination with severe systolic hypertension significantly increased the risk of dementia, AD, and VaD. The adjusted HRs related to the interaction term of severe systolic hypertension-by-diabetes were 3.0 (95% CI 1.4 to 6.4) for dementia, 2.6 (95% CI 1.0 to 6.8, $p = 0.05$) for AD, and 11.3 (95% CI 1.5 to 88.3) for VaD. Diabetes and heart disease had a synergistic effect on the risk of VaD. The adjusted HR of VaD related to the term of heart disease-by-diabetes was 7.8 (95% CI 1.1 to 62.6). There was no statistical interaction of diabetes with *APOE*-ϵ4 on the risk of AD (HR 1.0, 95% CI 0.3 to 2.9).

We also examined the combined effect of diabetes and stroke on dementia. Compared to subjects with neither diabetes nor stroke, the adjusted HRs of dementia were 1.2 (95% CI 0.8 to 1.8) for subjects with only diabetes, 1.6 (95% CI 1.2 to 2.2) for those with only stroke, and 2.6 (95% CI 1.3 to 5.0) for those with both diabetes and stroke. No statistical interaction of diabetes with stroke on the risk of dementia was present (HR 1.0, 95% CI 0.5 to 2.3).

In the supplementary analyses, similar results were obtained using only the second follow-up data (i.e., the dementia-free cohort that was identified at the first follow-up examination, n = 744, 126 dementia cases, 96 AD cases). Further, we repeated the analysis by leaving out the 53 subjects of those without blood glucose information, which produced the results that were much the same as those from the initial analysis. Finally, exclusion of those with "questionable dementia" from the analysis did not substantially alter the initial results (data not shown).

Discussion. In this community-based longitudinal study of persons aged 75 years and older, we found that 1) diabetes mellitus increased the risk of dementia, and VaD in particular, independent of other vascular factors; 2) there was no association between diabetes and risk of AD in the absence of *APOE*-ϵ4 allele or severe systolic hypertension (i.e., ≥180 mm Hg); and 3) there were synergistic effects of diabetes and severe systolic hypertension on the risk of dementia and its main subtypes, and of diabetes and heart disease on VaD.

Previous prospective studies show that diabetes is

Table 2 *Crude incidence rates (IR, per 1,000 person-years) and basic- and multi-adjusted HRs (95% CIs) of all types of dementia, Alzheimer disease, and vascular dementia by baseline diabetes mellitus, use of oral antidiabetic medications, and blood glucose level*

Characteristic	All types of dementia				Alzheimer disease				Vascular dementia			
	No.	IR	Basic-adjusted HR (95% CI)*	Multi-adjusted HR (95% CI)†	No.	IR	Basic-adjusted HR (95% CI)*	Multi-adjusted HR (95% CI)†	No.	IR	Basic-adjusted HR (95% CI)*	Multi-adjusted HR (95% CI)†
Diabetes mellitus												
No	313	60.6	1.0 (Ref.)	1.0 (Ref.)	237	47.8	1.0 (Ref.)	1.0 (Ref.)	42	9.5	1.0 (Ref.)	1.0 (Ref.)
Yes	37	88.9	1.5 (1.1–2.1)	1.5 (1.0–2.1)‡	23	61.2	1.3 (0.8–1.9)	1.3 (0.9–2.1)	7	21.7	2.2 (1.1–5.0)	2.6 (1.2–6.1)
Oral medication	17	97.4	1.7 (1.1–2.7)	1.7 (1.0–2.8)‡	9	60.7	1.2 (0.6–2.3)	1.4 (0.7–2.7)	5	34.1	3.3 (1.3–8.5)	3.6 (1.3–9.5)
Blood glucose§												
≤11 mmol/L	323	61.4	1.0 (Ref.)	1.0 (Ref.)	245	48.6	1.0 (Ref.)	1.0 (Ref.)	41	9.2	1.0 (Ref.)	1.0 (Ref.)
>11 mmol/L	13	93.0	1.5 (0.9–2.6)	1.6 (0.9–2.8)	7	53.4	1.1 (0.5–2.2)	1.2 (0.5–2.5)	5	44.5	4.4 (1.7–11.1)	7.4 (2.8–20.2)

* The hazard ratios (HRs) and 95% CIs were estimated after adjustment for age, sex, and education.

† The HRs and 95% CIs were estimated after adjustment for age, sex, education, heart disease, stroke, systolic blood pressure, diastolic blood pressure, antihypertensive drug use, and body mass index. The mean values of 155 mm Hg for systolic blood pressure and 81 mm Hg for diastolic blood pressure were used for the 31 subjects with missing blood pressure readings.

‡ $p = 0.04$.

§ Information on blood glucose was missing for 53 subjects, including five subjects with diabetes and 48 without diabetes.

Table 3 *Adjusted hazard ratios and 95% CIs of all types of dementia, Alzheimer disease, and vascular dementia for the combined effect of diabetes mellitus and high systolic blood pressure (SBP), heart disease, or APOE-ϵ4 allele*

Exposure status		All types of dementia		Alzheimer disease		Vascular dementia	
		No.	HR (95% CI)*	No.	HR (95% CI)*	No.	HR (95% CI)*
Diabetes	SBP,† mm Hg						
No	<180	252	1.0 (Ref.)	191	1.0 (Ref.)	33	1.0 (Ref.)
Yes	<180	21	1.1 (0.7–1.7)	16	1.1 (0.7–1.9)	4	1.2 (0.4–4.0)
No	≥180	53	0.9 (0.7–1.2)	42	1.0 (0.7–1.3)	5	0.7 (0.3–1.7)
Yes	≥180	13	2.8 (1.5–4.9)	6	2.8 (1.3–6.1)	2	9.2 (2.0–41.9)
Diabetes	Heart disease						
No	No	265	1.0 (Ref.)	208	1.0 (Ref.)	36	1.0 (Ref.)
Yes	No	28	1.5 (0.9–2.2)	19	1.5 (0.9–2.4)	3	1.6 (0.5–5.2)
No	Yes	48	1.2 (0.9–1.7)	29	1.0 (0.7–1.5)	6	1.0 (0.4–2.6)
Yes	Yes	9	1.6 (0.8–3.1)	4	1.1 (0.4–2.9)	4	6.3 (2.1–19.1)
Diabetes	*APOE*-ϵ4†						
No	No	157	1.0 (Ref.)	122	1.0 (Ref.)	17	1.0 (Ref.)
Yes	No	23	1.3 (0.9–2.1)	12	1.0 (0.5–1.8)	8	6.5 (2.5–17.2)
No	Yes	85	1.6 (1.2–2.1)	67	1.7 (1.2–2.3)	10	1.6 (0.6–3.2)
Yes	Yes	7	2.0 (0.9–4.3)	5	2.4 (1.1–6.1)	0	0.0 (0.0–0.0)

* The HRs and 95% CIs were estimated after adjustment for age, sex, education, body mass index, diastolic blood pressure, antihypertensive drug use, and stroke, and if applicable, for heart disease, SBP, and *APOE*-ϵ4 status.

† The numbers of subjects with missing values were 31 for blood pressure reading (3.5% of subjects with diabetes mellitus and 2.3% without the disease) and 316 for *APOE* genotypes (20.0% of subjects with diabetes mellitus and 24.2% of those without the disease).

associated with an elevated risk of dementia and VaD.[11-13,19,20] The relation between diabetes and dementia could be explained through vascular damages and nonvascular effects of diabetes. Diabetes is notorious for micro- and macrovascular complications, and is a well-established risk factor for cardiac and cerebrovascular diseases. VaD is characterized by small and large brain infarcts usually associated with vascular changes. Therefore, an increased risk of VaD resulting from diabetes can be expected. Despite this, there are indications that the effect of diabetes on dementia is not, or at least not entirely, mediated through vascular factors. Also, diabetic patients without clinical cerebrovascular disease were found to perform more poorly on cognitive tests than healthy controls.[38] In the CSHA, diabetes was associated with vascular cognitive impairment after adjusting for stroke, hypertension, and heart disease.[20] Diabetes may not only increase the burden of cerebrovascular disease through vascular damages but chronic hyperglycemia may exacerbate the existing cerebral ischemia through the increased anaerobic metabolism and acidotoxicity as well.[23] Our results indicated independent associations between diabetes mellitus and the risk of dementia and VaD. Further, a higher level of blood glucose was found to be associated with an increased risk for VaD, independently of other vascular diseases, suggesting that nonvascular pathways may be involved in the development of dementia. However, some vascular confounding effect caused by factors such as white matter lesions and silent brain infarcts might still be present even with these adjustments.[39] Neuroimaging or autopsy-verified studies are imperative to better understand the possible mechanisms of diabetes in AD and dementia. In addition, we found that oral medication users had a greater risk for developing dementia and VaD, probably because use of medications may reflect the severity of the disease.

We failed to find a relevant association between diabetes mellitus and AD risk, which is in agreement with the findings from the Swedish twins study,[19] the Canadian study,[20] the multiethnic cohort study in the United States,[22] and the Hisayama study,[40] but in disagreement with other studies.[11-13,18] Several reasons for this discrepancy can be considered. First, the age of the population in our study (≥75 years) as well as in the twins study (≥80 years) is much older than that of the Rotterdam study (≥55 years)[12] and the Rochester study (≥45 years).[11] The risk effect of diabetes on AD may be diminished in the very old due to, for example, selective survival. Second, the cohort of the Honolulu-Asia Aging Study (HAAS) consisted of Japanese-American men, and the Rochester study detected an association between diabetes and AD only in men. The fact that 76% of our population was women may explain why we did not find such an association. Third, the potential bias of an over-representation of mixed dementia or VaD cases in AD group was pointed out in both the Rotterdam and the Rochester studies. Finally, the finding of a diabetes–AD association in the Cambridge study was

based on a nested case-control design with only 18 AD cases.[18]

In the analysis of the combined effect between diabetes and vascular disorders on dementia, we found that subjects with both diabetes and severe systolic hypertension had a higher risk for developing dementia, AD, and VaD. This is in line with a recent study in which a strong interaction between diabetes and hypertension on cortical atrophy was reported.[41] Diabetes mellitus may also interact with either heart disease or stroke to greatly increase the risk of VaD and dementia. These results are in favor of the notion that a combination of multiple approaches such as lifestyle changes and use of appropriate drug regimens is of importance in the prevention of not only cardiovascular disease but also dementia.[42,43]

The *APOE*-ϵ4 is a well-established genetic risk factor for AD. A population-based cohort study showed that *APOE*-ϵ4 allele in combination with diabetes substantially increased the risk of cognitive decline.[24] The HAAS indicated a synergistic effect of diabetes and *APOE*-ϵ4 on the risk of AD, suggesting that *APOE*-ϵ4 could modify the effect of diabetes on AD.[13] We found that among non-carriers of *APOE*-ϵ4 allele, diabetes mellitus was not related to the risk of AD, while in the ϵ4 allele carriers diabetes tended to be related to a higher risk of AD. However, we were not able to verify the modifying effect of *APOE*-ϵ4 allele because of too few demented subjects with diabetes among the *APOE*-ϵ4 allele carriers.

The strengths of the present study are the community-based design, the relatively long-term follow-up period, and the adjustment for multiple potential confounders. However, our study has limitations. First, the study population consisted of individuals with a minimum age of 75 years at entry. As mortality risk is elevated in patients with diabetes mellitus,[44] the patients with most severe diabetes might have died before reaching this age. Consequently, the association between diabetes mellitus and dementia and its subtypes might have been underestimated in a very old population. Thus, our findings may not be generalizable to the younger population. Second, we were not able to separate type I and type II diabetes. However, old adults mostly have type II diabetes, and patients with type I diabetes could not survive up to this old age.[25] Third, the diabetes diagnosis was not accurate as in a clinical setting, although we tried to define the disease through a combination of information sources. This non-differential misclassification will generally lead to an underestimation of a given diabetes–dementia association. Finally, the diagnosis of dementia and its subtypes was made clinically. However, the clinical assessment for dementia was comprehensive and precise in our project.[34] Even if neuroimaging is available, these data may help to find vascular lesions, but cannot determine whether these lesions are causative, as coexistence of AD pathologic changes and vascular lesions in the brain is fairly common in very old people[45] and it is often difficult to determine which contributes more to the development of the disease.

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