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Diabetes, Alzheimer disease, and vascular dementia

A population-based neuropathologic study

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ABSTRACT

Objective: To investigate the relation of diabetes to dementia, Alzheimer disease (AD), and vascular dementia (VaD), through analyses of incidence, mortality, and neuropathologic outcomes in a prospective population-based study of the oldest old.

Methods: The Vantaa 85+ study included 553 residents living in the city of Vantaa, Finland, and aged ≥85 years on April 1, 1991. Survivors were reexamined in 1994, 1996, 1999, and 2001. Autopsies were performed in 291 persons who died during the follow-up (48% of total population). Diabetes was assessed according to self-report, medical record of physician-diagnosed diabetes, or use of antidiabetic medication. Macroscopic infarcts were identified from 1-cm coronal slices of cerebral hemispheres, 5-mm transverse brainstem slices, and sagittal cerebellum slices. Methenamine silver staining was used for β-amyloid, methenamine silver-Bodian staining for neurofibrillary tangles, and modified Bielschowsky method for neuritic plaques. Cox proportional hazards and multiple logistic regression models were used to analyze the association of diabetes with dementia and neuropathology, respectively.

Results: Diabetes at baseline doubled the incidence of dementia, AD, and VaD, and increased mortality. Individuals with diabetes were less likely to have β-amyloid (hazard ratio [HR] [95% confidence interval (CI)] was 0.48 [0.23–0.98]) and tangles (HR [95% CI] 0.72 [0.39–1.33]) but more likely to have cerebral infarcts (HR [95% CI] 1.88 [1.06–3.34]) after all adjustments.

Conclusion: Elderly patients with diabetes develop more extensive vascular pathology, which alone or together with AD-type pathology (particularly in *APOE* ε4 carriers) results in increased dementia risk. ***Neurology*® 2010;75:1195–1202**

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; **HR** = hazard ratio; **NFT** = neurofibrillary tangles; **OR** = odds ratio; **VaD** = vascular dementia.

Population-based longitudinal studies have shown that diabetes is an independent risk factor for dementia[1] and its main subtypes Alzheimer disease (AD)[1–3] and vascular dementia (VaD),[3–5] but also controversial findings have been reported.[6,7] Some biologic mechanisms have been postulated through which diabetes might increase the risk of AD: vascular mechanisms, toxic effects of hyperglycemia, insulin resistance of the brain, formation of advanced glycation end products, and competition for insulin-degrading enzyme resulting in reduced degradation of β-amyloid, but none of these has been proven unequivocally. As diabetes is known to increase cerebrovascular disease,[8] its association to VaD is understandable. Several studies have reported a greater risk and faster rate of cognitive decline in patients with type 2 diabetes.[9,10] Amyloid plaques and neurofibrillary tangles (NFT) are the neuropathologic hallmarks of AD. Evaluating differences in quantity of these outcomes between diabetic and nondiabetic subjects might shed light on the mechanisms behind the

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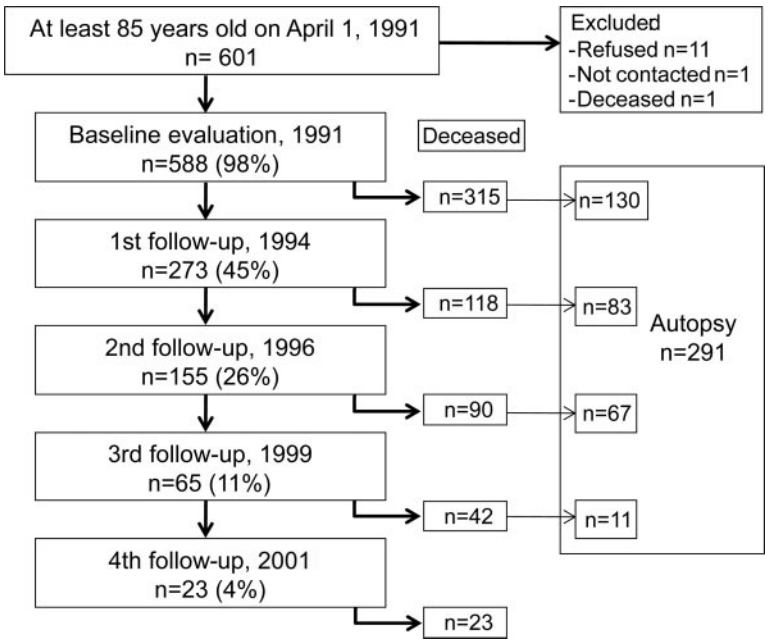
Figure 1 Flow chart of the Vantaa 85+ study population



epidemiologic connections reported. Patients with AD and diabetes have a markedly higher mortality when compared to nondiabetic patients with AD.[11] The aim of this study was to investigate the associations of diabetes with dementia and its main subtypes through analyses of incidence, mortality, and neuropathologic outcomes in a prospective population-based study of people aged at least 85 years.

METHODS

Participants. All residents living in the city of Vantaa in Southern Finland (including those institutionalized) and aged ≥85 years on April 1, 1991, were invited to participate in the Vantaa 85+ study. Figure 1 depicts formation of the study population. Baseline health information was obtained from 588 individuals who gave informed consent. Of these, 35 died before the baseline clinical evaluation. Thus, 553 individuals participated in the baseline clinical evaluations conducted between April 1, 1991, and March 12, 1992. Survivors were reexamined in 1994, 1996, 1999, and 2001. Clinical evaluations included a structured general and neurologic examination performed by a neurologist and a public health nurse trained for the study methodology. The entire study population is now deceased. The database includes information on 291 autopsies and brain examinations, including data on Alzheimer-type pathology and cerebral infarcts.

Standard protocol approvals, registrations, and patient consents. The Vantaa 85+ study was approved by the Ethics Committee of the Health Centre of the city of Vantaa. Participants gave written informed consent before enrollment in the study. Permission for autopsy was obtained from the closest relative in all cases.

Clinical assessment. Diabetes was assessed according to self-report or medical record of diabetes diagnosed by a physician or use of oral antidiabetic medication or insulin. Individuals were classified as having diabetes if diagnosis of diabetes was found at baseline or during follow-up. History of cardiovascular risk factors and conditions (i.e., hypertension, hypercholesterolemia, myocardial infarction, heart failure, atrial fibrillation) was assessed using data obtained from interviews, previous health records, clinical assessment at baseline, and determination of serum total cholesterol.

Diagnosis of dementia. Individuals were considered to have dementia if they fulfilled criteria of *DSM-III-R*[12] and the duration of dementia symptoms was at least 3 months. Assessments were based on data obtained from interviews, health examinations, previous health and social work records, and tests of cognitive function and functional capacity. The National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders Association[13] criteria were used for clinical diagnosis of AD and criteria of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences[14] criteria were used for clinical diagnosis of VaD. Clinical dementia diagnoses were made as consensus by 2 neurologists. All health and social work records were examined to identify new dementia cases among people who died before April 1, 2001, and were free of dementia at baseline and follow-ups. Onset of a dementia disorder was defined as onset of the first disturbing symptoms (usually memory problems) reported by relatives or caregivers, or detected in health records. Few individuals were diagnosed with dementia without evidence of previous dementia symptoms. On these rare occasions, dementia onset was timed at the midpoint between the preceding and current visit. The point prevalence of clinically diagnosed dementia on April 1, 1991, was calculated based on all available previous documentation.

For *APOE* genotyping, 2 methods, DNA mini-sequencing[15] and DNA amplification with PCR followed by restriction enzyme digestion with *Hha*I,[16] were independently used in 2 laboratories (Department of Medicine, University of Helsinki, Finland, and Mayo Clinic, Jacksonville, FL) with identical results. In 16 individuals, only 1 method was used due to limited available DNA amount. *APOE* genotyping was available for 532 participants clinically examined at baseline.

Neuropathology. Gross and microscopic examinations were performed by one pathologist blinded to all clinical data. Clinical information and autopsy report were not available at brain dissection. The same dissection and examination protocol was used for each brain. The sampling procedure, quantitation of β-amyloid protein deposition, and NFT counting were previously described in detail.[17]

Brains of autopsied individuals (n = 291) were fixed in phosphate-buffered 4% formaldehyde solution for at least 2 weeks before specimens were obtained from the middle frontal, superior temporal, and middle temporal gyri and inferior parietal lobule, according to the Consortium to Establish a Registry for Alzheimer's Disease protocol for diagnosis of AD.[18] Paraffin sections were cut at a thickness of 8 μm for staining with methenamine silver for β-amyloid protein[19] and 10 μm for staining with methenamine silver-Bodian stain for NFTs,[20] and with modified Bielschowsky method for NPs. Methenamine silver staining has been shown to be as sensitive as β-amyloid protein immunostaining for detecting senile plaques, including diffuse plaques.[19,21]

To estimate the amount of β-amyloid protein deposited in the cerebral cortex, the fraction of cortical specimens covered by methenamine silver-stained plaques was quantified.[22] The con-

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tiguous cortical microscopic fields, extending from the pial surface to the white matter, were examined, at a magnification of 100× with a square microscopic graticule, 1.25 mm in width, along a line perpendicular to the pial surface. The graticule consisted of 10 horizontal and 10 vertical lines with 100 intersections. All intersections that overlay a methenamine silver-positive plaque were counted. In every specimen at least 7 (maximum 10) cortical columns (width 1.25 mm) were examined from the pial surface to the white matter. The fraction of cortex covered by plaques was determined by dividing the number of intersections overlying a methenamine silver-positive plaque by the total number of cortical intersections. The average fraction of cortex covered by methenamine silver-positive plaques was calculated for all 4 specimens from each individual to minimize the effect of variations in extent of β-amyloid protein deposition in different brain regions. The final value (expressed as percentage) provided an estimate of the extent of β-amyloid protein deposition in the cerebral cortex.

After methenamine silver-Bodian staining, the NFTs were counted in contiguous cortical microscopic fields, extending from the pial surface to the white matter, at a magnification of 200× with a square microscopic counting frame, 0.55 mm in width, along a line perpendicular to the pial surface. All NFTs totally inside the frame or hitting the left side of the frame were counted. In every specimen, 10 cortical columns (width 0.55 mm) were examined from the pial surface to the white matter. The average number of NFTs counted per cortical specimen was determined by dividing the total number of NFTs in all 4 cortical specimens by 4.

Cavitary lesions or solid cerebral infarcts visible to the naked eye were identified by examination of the intact brain and from 1-cm-thick coronal slices of the cerebral hemispheres, from 5-mm-thick transverse slices of the brainstem, and sagittal slices of the cerebellum. All lesions were subsequently histologically ascertained to be infarcts.

Statistical analyses. Baseline demographic characteristics of individuals with and without diabetes were compared with *t* tests for continuous variables and Fisher exact test for proportions. Education was categorized into a binary variable using the median of 4 years. A dichotomous variable was created to indicate presence/absence of cardiovascular risk factors or conditions.

Individuals with dementia at baseline were excluded from analyses of dementia incidence. The baseline date was set as April 1, 1991, when each individual's dementia status was defined and the point prevalence calculated. The end of the follow-up time was set at the date of dementia diagnosis or death. Incidence of dementia among individuals with and without diabetes was estimated with Kaplan-Meier estimator. In univariate analyses, the difference between incidence rates was tested with the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HR) for dementia development. In multivariate analyses, baseline age, gender, education level, and the presence of at least one *APOE* ϵ4 allele were included as covariates in Cox models.

In analyses of neuropathologic findings, logistic regression models were used to compare the presence of β-amyloid, NFTs, and cerebral infarcts in individuals with and without diabetes. In adjusted analyses, gender, age at death, presence of *APOE* ϵ4, and dementia status were considered as covariates. In addition to analyses of neuropathologic findings as dichotomous variables, Mann-Whitney rank-sum test was used to compare the groups regarding the fraction of cortex covered by methenamine silver-positive plaques, number of NFTs, and number of cerebral infarcts.

Mortality rates during follow-up by dementia status in individuals with and without diabetes were analyzed by Kaplan-Meier estimator, and log-rank test was used to assess statistical

Table 1 Characteristics of the whole study population and the autopsy subpopulation[a]

	Whole study population			Neuropathology population		
	No diabetes	Diabetes	p[b]	No diabetes	Diabetes	p[b]
No. (%)	457 (77.7)	131 (22.3)		221 (76.0)	70 (24.1)	
Age at baseline, y, mean (SD)	88.5 (3.0)	87.9 (2.6)	0.024	88.9 (3.2)	88.2 (2.8)	0.069
Age at death, y, mean (SD)	92.4 (4.0)	91.3 (3.2)	0.007	92.4 (3.9)	91.4 (2.8)	0.048
Female	78.3	84.0	0.177	81.5	90.0	0.100
Education >4 y	23.9 (n = 376)	19.6 (n = 112)	0.373	27.0 (n = 174)	16.1 (n = 62)	0.119
Cardiovascular disease	74.8 (n = 385)	86.0 (n = 114)	0.015	76.5 (n = 187)	84.6 (n = 65)	0.219
APOE ϵ4	31.7 (n = 413)	21.5 (n = 121)	0.031	32.5 (n = 200)	26.1 (n = 69)	0.366
Dementia at baseline	41.4	33.6	0.128	48.4	35.7	0.074
Dementia at death	56.9	56.5	1.000	65.9	60.0	0.381
Alzheimer disease at baseline	19.3	11.5	0.038	24.0	11.4	0.028
Alzheimer disease at death	27.1	23.7	0.500	33.9	24.3	0.142
Vascular dementia at baseline	19.0	21.4	0.535	19.9	22.9	0.613
Vascular dementia at death	23.9	30.5	0.138	24.4	35.7	0.089
Stroke (clinical) at baseline	20.2	22.1	0.625	19.0	22.9	0.495
Stroke (clinical) at death	26.3	29.8	0.436	25.3	30.0	0.441

[a] Values are percentages unless stated otherwise.
[b] *p* Values: Fisher exact test for categorical variables and Student *t* test for continuous variables.

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significance. Cox proportional hazards models were used to estimate HRs for mortality. Individuals with missing data were excluded from analyses.

Analyses were done using SPSS for Windows 15.0 (SPSS Inc., Chicago, IL) and Stata 9.2 (StataCorp, College Station, TX).

RESULTS **Population characteristics.** Formation of the study population is shown in figure 1 and demographic and clinical characteristics in table 1. Of the 588 persons included in this study, 79.6% were female, 22.3% had diabetes, and 39.6% had dementia at baseline. Diabetic patients compared with nondiabetic people more often had heart failure (78.6% vs 57.1%, $p < 0.001$) and hypertension (33.9% vs 23.4%, $p = 0.028$) at baseline but there were no significant differences between groups regarding other cardiovascular risk factors or conditions.

Diabetes and dementia. In cross-sectional analyses at baseline, diabetes was not related to dementia, AD, or VaD after adjusting for gender, age, education, cardiovascular conditions, and *APOE* ϵ4. No significant interactions between *APOE* ϵ4 and diabetes were found for prevalent dementia.

Incidence of dementia in people free of dementia at baseline (n = 355) was twice as high in diabetic then nondiabetic people even after adjustments for age, gender, education, and *APOE* ϵ4 status (table 2). Gender-stratified analyses showed higher incidence of dementia in diabetic compared to nondiabetic women: adjusted HR (95% confidence interval [CI]) 2.31 (1.43–3.71) but not men: 1.11 (0.28–4.33). However, the small number of men makes it difficult to draw conclusions on gender differences. In people carrying the *APOE* ϵ4 allele, dementia incidence was nearly 4 times higher in diabetic compared to nondiabetic persons even after adjustments for age, gender, and education (figure 2). Diabetic compared to nondiabetic subjects had twice as high incidence of both AD (adjusted HR [95% CI] 2.45 [1.33–4.53]) and VaD (2.15 [1.06–4.36]) after all adjustments.

Diabetes and mortality. In the entire population, diabetic patients compared with nondiabetic people had increased mortality: HR (95% CI) was 1.30 (1.07–1.59). In stratified analyses by dementia status, diabetes increased mortality in people without dementia: HR (95% CI) 1.38 (1.07–1.77) but not significantly for patients with dementia: HR (95% CI) 1.21 (0.85–1.71).

Diabetes and neuropathology. In neuropathologic analyses, the proportion of individuals with β-amyloid and NFTs was lower in diabetic compared to nondiabetic people; for β-amyloid, this difference was significant (table 3). The proportion of individuals with cerebral infarctions was significantly higher in diabetic compared to nondiabetic people. Individuals with diabetes were less likely to have β-amyloid and NFTs but more likely to have cerebral infarcts after adjustments for age at death, gender, education, *APOE* ϵ4, and dementia status. Stratified analyses by dementia status showed similar patterns of association for diabetes: in persons without dementia, adjusted ORs (95% CI) were 0.68 (0.24–1.91) for amyloid, 0.44 (0.16–1.19) for NFTs, and 3.27 (1.14–9.33) for cerebral infarcts (table e-1 on the *Neurology*® Web site at www.neurology.org). In patients clinically diagnosed with AD, adjusted ORs (95% CI) were 0.04 (0.00–0.41) for amyloid, 0.76 (0.18–3.21) for NFTs, and 0.59 (0.17–2.10) for cerebral infarcts, as expected due to AD criteria excluding significant vascular disease (table e-2).

Table 2 Incidence of dementia by diabetes status and *APOE* ϵ4 status

	All individuals			Without *APOE* ϵ4			With *APOE* ϵ4		
	No diabetes	Diabetes	p	No diabetes	Diabetes	p	No diabetes	Diabetes	p
No. of subjects (%)	268 (75.5)	87 (24.5)		194 (74.3)	67 (25.7)		56 (81.2)	13 (18.8)	
Person-years of follow-up	1,045	257		820	218		201	34	
Incident dementia	75	31		54	21		20	10	
Incidence per 100 person-years (95% CI)	7.2 (5.7-9.0)	12.1 (8.5-17.2)		6.6 (5.0-8.6)	9.6 (6.3-14.8)		10.0 (6.4-15.4)	29.2 (15.7-54.2)	
Hazard ratio, unadjusted (95% CI)	1.0	1.77 (1.14-2.74)	0.011	1.0	1.51 (0.90-2.54)	0.121	1.0	3.51 (1.54-8.00)	0.003
Hazard ratio, adjusted[a] (95% CI)	1.0	2.09 (1.34-3.25)	0.001	1.0	1.68 (0.99-2.83)	0.053	1.0	3.80 (1.69-8.53)	0.001

Abbreviation: CI = confidence interval.
[a] Adjusted for age at baseline, gender, education, and *APOE* ϵ4 status.

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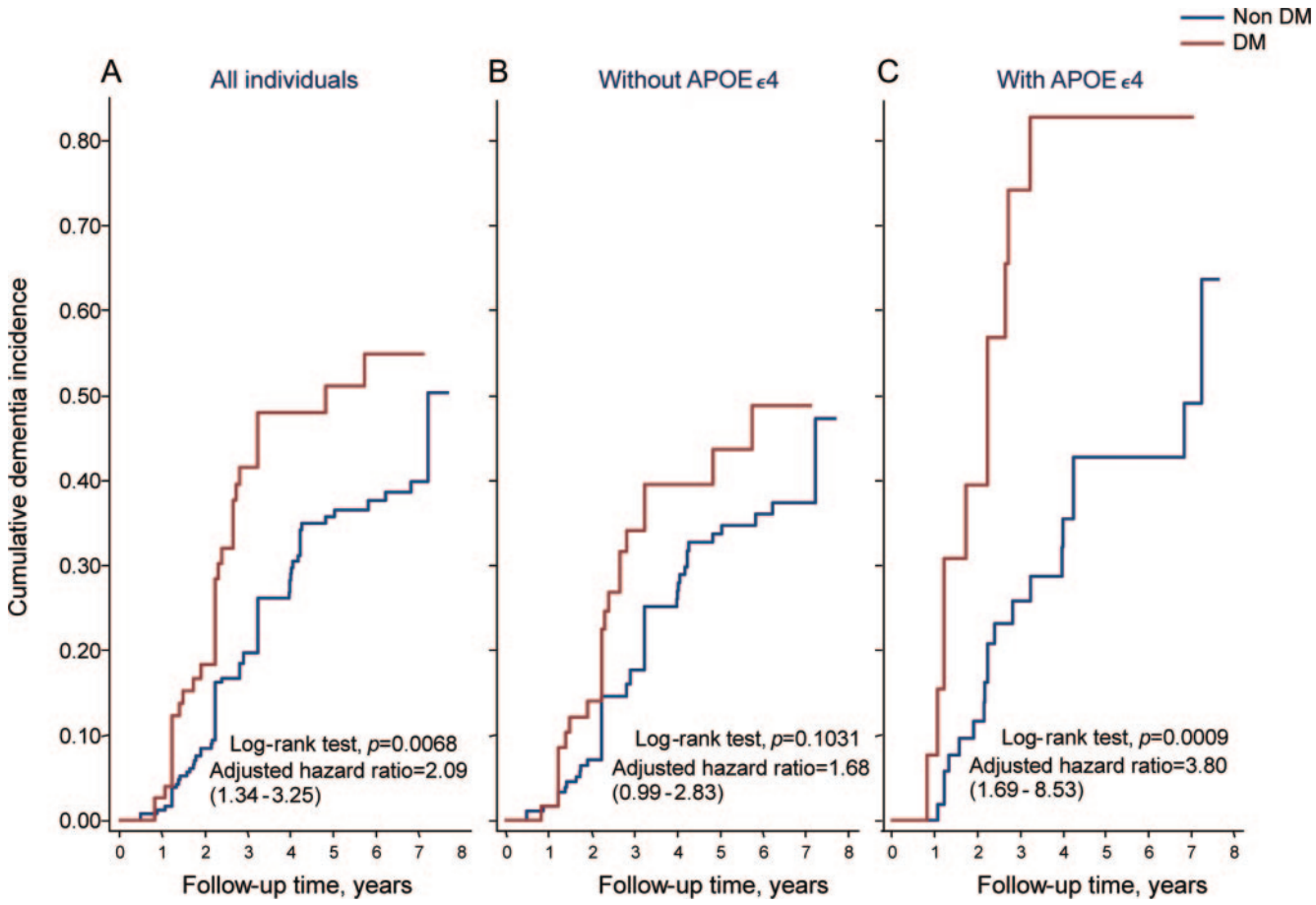
Figure 2 Cumulative dementia incidence



(A) Whole population free of dementia at baseline. (B) Population free of dementia at baseline not carrying an *APOE* ϵ4 allele. (C) Population free of dementia at baseline carrying an *APOE* ϵ4 allele. Adjusted for age at baseline, gender, education, and *APOE* ϵ4 status.

Carrying at least one *APOE* ϵ4 allele increased the risk of β-amyloid and NFTs, but not cerebral infarcts. No significant interactions were found between diabetes and *APOE* ϵ4 in relation to neuropathologic outcomes. People with a longer duration of dementia were more likely to have β-amyloid, but adding duration of dementia into the model did not change the diabetes–β-amyloid relation. Duration of dementia was not a significant predictor for presence of NFTs or cerebral infarcts.

Findings of β-amyloid at brain autopsy were related to the clinical AD diagnosis: odds ratio (OR) (95% CI) 3.48 (1.19–10.18), and all dementia: 3.12 (1.48–6.57), but not VaD: 1.28 (0.56–2.94). NFTs at autopsy were related to clinical diagnoses: for AD: OR (95% CI) 2.91 (1.41–6.01), all dementia: 1.92 (1.06–3.47), and VaD: 0.86 (0.44–1.69). Cerebral infarcts were associated with clinical VaD diagnosis: OR (95% CI) 2.26 (1.19–4.27) and all dementia: 1.78 (1.01–3.15), but not AD: 1.01 (0.55–1.85).

DISCUSSION This population-based clinical-pathologic study of the oldest old found that diabetes doubled dementia incidence and increased mortality and risk of cerebral infarctions, but was related to less amyloid accumulation. These results suggest that the increased dementia incidence in very elderly diabetic patients might not primarily be explained by an increase in AD-type neuropathology, but rather by an increase in vascular brain pathology. Cerebrovascular lesions are known to play an important role in determining the presence and severity of the clinical symptoms of AD.[23] Fewer AD neuropathologic lesions are needed to produce dementia in people who also have cerebrovascular lesions.[23]

In our study, dementia duration was shorter in diabetic compared to nondiabetic people (probably due to the diabetes-related increase in mortality), but this was insufficient to fully explain group differences in neuropathology. Also, controlling or stratifying analyses for dementia status did not change the patterns of association between diabetes and neuropathology. Clinical dementia diagnoses correlated well with brain autopsy findings, which reduces the probability of misclassification of dementia cases. How-

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Table 3 Relationship of diabetes to neuropathologic findings

	Amyloid			Tangle			Cerebral infarct		
	Non-DM	DM	p^a	Non-DM	DM	p^a	Non-DM	DM	p^a
No. (%)	221 (76.0)	70 (24.1)		216 (76.3)	67 (23.7)		193 (74.2)	67 (25.8)	
Proportion with >0	86.4	74.3	0.025	66.7	58.2	0.242	44.6	59.7	0.034
Median	2.9	2.3	0.319	0.5	0.5	0.661	0	1	0.151
DM vs non-DM, OR (95% CI)									
Crude	0.45 (0.23–0.88)		0.019	0.70 (0.40–1.22)		0.208	1.84 (1.05–3.25)		0.034
Model 1[b]	0.43 (0.22–0.84)		0.013	0.71 (0.40–1.26)		0.241	1.78 (1.00–3.17)		0.051
Model 2[c]	0.38 (0.19–0.76)		0.006	0.67 (0.36–1.23)		0.196	1.61 (0.87–2.99)		0.130
Model 3[d]	0.39 (0.19–0.82)		0.013	0.69 (0.36–1.32)		0.266	1.63 (0.87–3.08)		0.129
Model 4[e]	0.48 (0.23–0.98)		0.045	0.72 (0.39–1.33)		0.295	1.88 (1.06–3.34)		0.031

Abbreviations: CI = confidence interval; DM = diabetes mellitus; OR = odds ratio.
[a] *p* Values: Proportions: Fisher exact. Medians: Mann-Whitney rank sum nonparametric test.
[b] Model 1: Adjusted for gender and age at death.
[c] Model 2: Adjusted for factors in model 1 and for education.
[d] Model 3: Adjusted for factors in model 2 and for *APOE* ϵ4.
[e] Model 4: Adjusted for all factors significant in earlier models. **Amyloid:** Diabetes, dementia diagnosis ever, and *APOE* ϵ4 status. **Tangle:** Diabetes, dementia diagnosis ever, and *APOE* ϵ4 status. **Cerebral infarct:** Diabetes at baseline and dementia diagnosis ever.

ever, current diagnostic criteria for dementia are known to have a bias toward AD[24] and AD diagnostic criteria do not acknowledge the contribution of vascular pathology, particularly small cerebrovascular lesions.

An earlier study in younger elderly found a similar negative association between diabetes and AD neuropathology, reporting that persons with diabetes had fewer NPs and NFTs in the cerebral cortex and lower plaque ratings in the hippocampus compared to persons without diabetes.[25] In another study, dementia was associated with greater amyloid load and free radical damage in nondiabetic persons, but with microvascular infarcts and neuroinflammation in diabetic patients.[26] Four other studies found no relation between diabetes and AD neuropathology.[27–30] A positive association was reported only in one study where people with both diabetes and the *APOE* ϵ4 allele had higher numbers of hippocampal NPs and hippocampal and cortical NFTs.[2] Differences in results between studies could be due to methodologic and population differences. Age is particularly important, as the association between AD pathology and dementia is stronger in younger old compared to older old persons.[31] The rise in NP and NFT densities seen in people who are 60 to 80 years old and transition from normal cognition to dementia is not observed in nonagenarians and centenarians with similar levels of dementia.[32] Previous studies on diabetes and neuropathology included subjects up to 86 years old at the time of death, while the average age at death in the Vantaa 85+ autopsy population was over 91 years.

Even in this very old population, carrying even one *APOE* ϵ4 allele increased the risk of dementia, AD, and VaD. *APOE* ϵ4 was also associated with increased risk of β-amyloid and NFTs. Diabetic patients with *APOE* ϵ4 had a significantly increased incidence of dementia, AD, and VaD compared with diabetic patients without *APOE* ϵ4, but no significant interactions between *APOE* ϵ4 and diabetes were found regarding dementia incidence or neuropathologic outcomes. It has, however, been previously reported that having both diabetes and the *APOE* ϵ4 allele can increase AD risk to a greater extent than the sum of each risk factor would lead to expect,[33] i.e., that they might operate synergistically for AD.

The major strength of this study is its prospective population-based design and relatively large sample size. The entire Vantaa 85+ study population comprised 98% of the people aged 85 years or above living in a geographically well-defined area, and the autopsy rate was also high, 48%. Quantitative, systematic methods were used to identify AD pathology. Diagnosis of diabetes was obtained from several sources and the longitudinal nature of the study ensured that those with severe forms of diabetes were included in analyses.

Among limitations, no biochemistry was used to identify diabetes and no data on diabetes duration, glycemic control, or insulin levels were available.

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Thus, the effect of diabetes severity could not be assessed. There may have been several people with undiagnosed diabetes in the group classified as nondiabetic which might have contributed to the negative association reported in the neuropathologic part of the study. Earlier studies have reported that both borderline and uncontrolled diabetes also increase the risk of AD.[34] Immunohistochemical methods are currently available for investigating β-amyloid; however, only conventional neuropathology methods were available at the time of this study.

The results of this study are in line with earlier findings in younger elderly populations that diabetes and *APOE* ε4 carrier status increase the risk of dementia, and extend this observation to the very elderly population. Our results suggest that the relation between diabetes and clinical AD diagnosis may not be fully explained by an increase in AD-type neuropathology. Instead, it is more likely that diabetic elderly people develop more extensive microvascular pathology, which alone or together with AD-type pathology, particularly in *APOE* ε4 carriers, results in an increased risk of clinical dementia. The neuropathologic processes leading to dementia among elderly patients with diabetes as well as the role of insulin resistance in the diabetes–dementia association need to be further clarified.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. S. Ahtiluoto and Dr. M. Peltonen. Dr. S. Ahtiluoto is the Guarantor.

DISCLOSURE

Dr. Ahtiluoto, Dr. Polvikoski, Dr. Peltonen, and Dr. Solomon report no disclosures. Dr. Tuomilehto has served on scientific advisory boards for AstraZeneca, Bayer Schering Pharma, and Novo Nordisk; has received funding for travel or speaker honoraria from AstraZeneca, Unilever, Bayer Schering Pharma, Boehringer Ingelheim, Pfizer Inc., Eli Lilly and Company, Merck Serono, Novartis, Sanofi-Aventis, Takeda Pharmaceutical Company Limited, Schering-Plough Corp., Novo Nordisk, DeveloGen AG, Leiras, Ranbaxy Laboratories Limited, and Merck Sharp & Dohme; serves on the editorial advisory boards of the *International Diabetes Monitor*, the *Croatian Medical Journal*, *Diabetes and Vascular Disease Research*, *Vascular Health and Risk Management*, *Current Hypertension Reviews*, *Diabetes and Metabolism Reviews and Research*, *The Open Cardiovascular Medicine Journal*, the *Iranian Journal of Public Health*, and *Diabetes Research and Clinical Practice,* and as an Associate Editor for the *European Journal of Clinical Nutrition*, the *European Journal of Epidemiology*, *Neuroepidemiology*, and the *European Journal of Clinical Investigation*; holds stock in Orion Corporation; and has given expert testimony on behalf of Pfizer Inc. Dr. Winblad has served on scientific advisory boards for Pfizer Inc., Medivation, Inc., Merz Pharmaceuticals, LLC, Janssen, Novartis, Roche, Lundbeck Inc., and Merck Sharpe & Dohme; serves on the editorial boards of the *American Journal of Alzheimer's Disease & Other Dementias*, the *Journal of Cellular and Molecular Medicine*, *Alzheimer's Care Today*, *Alzheimer's & Dementia*, *Dementia and Geriatric Cognitive Disorders*, the *International Journal of Geriatric Psychiatry*, and *Aging Clinical and Experimental Research*; receives institutional research support through Karolinska Institute from Dainippon Sumitomo Pharma; and has received research support from the Swedish Medical Research Council and Swedish Brain Power. Dr. Sulkava has received speaker honoraria from Novartis and has received research support from the Academy of Finland. Dr. Kivipelto has served on scientific advisory boards for Elan Corporation and Pfizer Inc.; served on the editorial board of the *Journal of Alzheimer's Disease*; and has received speaker honoraria from Janssen, Novartis, and Pfizer Inc.

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Diabetes, Alzheimer disease, and vascular dementia: A population-based neuropathologic study

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