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Predictors of cognitive impairment and dementia in older people with diabetes

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Abstract

Aims/hypothesis Diabetes is associated with an increased risk of dementia but the reasons for this association are unclear because there are many potential mechanisms. We explored the relative contribution of diabetes-related variables as predictors of dementia in older individuals with diabetes.

Methods Survivors, aged ≥70 or more, were recruited from an existing observational cohort study 7.6±1.0 years after baseline, when they underwent a comprehensive assessment of diabetes, complications and cardiovascular risk factors. Dementia, probable Alzheimer's disease and cognitive impairment without dementia were diagnosed clinically. Logistic regression modelling determined independent predictors of cognitive diagnoses.

Results Of 302 participants, aged 75.7±4.6 years, 28 (9.3%) had dementia (16 with probable Alzheimer's disease) and 60 (19.9%) had cognitive impairment without dementia. The major independent longitudinal predictors of dementia were older age (per decade; odds ratio 4.0, 95% CI 1.59–10.10), diabetes duration (for each 5 years; odds ratio 1.69, 95% CI 1.24–2.32), peripheral arterial disease (odds ratio 5.35, 95% CI 2.08–13.72) and exercise (which was protective; odds ratio 0.26, 95% CI 0.09–0.73). For Alzheimer's disease, diabetes duration was an independent predictor in addition to age and diastolic blood pressure. The results of the cross-sectional analyses were similar with respect to diabetes duration and peripheral arterial disease.

Conclusions/interpretation Peripheral arterial disease is a strong independent risk factor for dementia in diabetes. After adjustment for a wide range of potential risk factors, diabetes duration remains independently associated with dementia and probable Alzheimer's disease, indicating that factors not measured in this study may be important in the pathogenesis of dementia in diabetes.

Keywords Diabetes · Ageing · Dementia · Alzheimer's disease · Cerebrovascular disease

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Abbreviations

AD	Alzheimer's disease
Apo	apolipoprotein
CVD	cerebrovascular disease
FDS	Fremantle Diabetes Study
MMSE	Mini-Mental State Examination
PAD	peripheral arterial disease

Introduction

Studies from various populations have consistently shown diabetes to be associated with cognitive deficits and dementia [1–3]. The pathophysiological mechanisms underlying this association are not fully understood, mainly because of the wide range of possible aetiologies. Cerebrovascular disease is likely to be relevant given the significant role it plays in the development of Alzheimer's disease (AD) and vascular dementia [4]. Cardiovascular risk factors and atherosclerosis are also associated with dementia and AD [5–7] and the combination of diabetes and hypertension confers a high risk of dementia [8, 9]. In addition, non-vascular mechanisms may also contribute to dementia in diabetes [10], including excess formation of advanced glycation end-products [11] and/or disturbed neuronal insulin signalling that may promote cerebral amyloidosis [12].

In epidemiological studies exploring risk factors for dementia, associations between hyperglycaemia [9, 13] and insulin therapy [14, 15] have been reported and long-duration diabetes was associated with major cognitive decline [16]. However, these studies have a number of limitations that include adopting methods to diagnose diabetes subject to significant false negative rates [8, 9, 15, 16], incomplete or absent assessments of glycaemic control [5, 8, 9, 14–16] and lack of assessment of microvascular complications [5, 8, 9, 14–16]. In type 2 diabetes, glycaemic control, diabetic complications and the need for insulin treatment are strongly interrelated and in addition they are each related to the duration of diabetes. This means that the study of risk factors for dementia due to diabetes requires that these factors, as well as other suggested cardiovascular and diabetes-related factors, are measured together.

In the present study, we examined risk factors for dementia, cognitive impairment without dementia, dementia and AD in older diabetic participants drawn from an observational study representative of the Australian diabetic community, in whom comprehensive longitudinal data were available. We distinguished participants with cognitive impairment who were not demented in the sample to increase analytical precision, and we distinguished dementia due to AD, given the controversy about whether diabetes increases the risk of AD [5, 8].

Methods

Patients We invited surviving participants of the Fremantle Diabetes Study (FDS), who were aged 70 years or more, to participate. The FDS recruited patients between 1993 and 1996, and annual assessments were performed until 2001. Details of recruitment procedures and the characteristics of the sample have been described previously [17, 18].

Between 1 February 2001 and 31 December 2002, 302 of the 587 FDS patients who were alive at the beginning of this period (51.4%) agreed to participate after being approached by letter and telephone [19]. Of the remaining 285, 66 (23.2%) had died before recruitment, 71 (24.9%) could not be contacted and 148 (51.9%) declined participation. Of this latter group, 45% cited health reasons, including dementia, as reasons for non-participation. The Human Rights Committee of Fremantle Hospital approved the study. All participants gave written, informed consent to participation in the study.

Baseline clinical assessment At the baseline assessment between 1993 and 1996, a comprehensive sociodemographic and clinical history was taken, a physical examination was performed and fasting blood and urine samples were collected for biochemical tests, including serum glucose, HbA_{1c}, lipoproteins, urinary albumin:creatinine ratio [20] and apolipoprotein E (ApoE) genotype.

Complications were identified using standard definitions. Peripheral sensory neuropathy was defined as a score of >2/8 on the clinical portion of the Michigan Neuropathy Screening Instrument [21]. Retinopathy was defined as any grade of retinopathy detected by direct and/or indirect ophthalmoscopy in one or both eyes and/or more detailed assessment by an ophthalmologist. Nephropathy was defined as a urinary albumin:creatinine ratio ≥3.0 mg/mmol in an early morning urine sample [22]. Self-reported stroke and transient ischaemic attack were amalgamated with prior hospitalisations for these conditions to define baseline cerebrovascular disease (CVD). CHD was defined if there was a self-reported history of (or hospitalisation for) myocardial infarction, angina, coronary artery bypass grafting, angioplasty, and/or definite myocardial infarction on a Minnesota coded electrocardiograph [20]. The ankle/brachial index was obtained from brachial and ankle systolic blood pressures using Doppler detection. Peripheral arterial disease (PAD) was defined as an ankle:brachial index ≤0.90 or the presence of a diabetes-related lower-extremity amputation [23]. Depression was assessed with a depression symptom questionnaire previously shown to diagnose depression in participants with type 2 diabetes with 83.3% sensitivity and 94.5% specificity [24].

Annual reviews FDS recruits were asked to attend for subsequent annual reviews for a possible 5 years from baseline, during which information was updated. These additional data, combined with data collected, at baseline and at the time of cognitive assessments provided, a mean (±SD) of 7±2 values for HbA_{1c} and BP in the sample.

Cognitive assessment This was conducted in 2001 and 2002. The FDS assessment template was followed with

some modifications. Incident CVD and CHD were ascertained by self-report supplemented by scrutiny of hospital records. The questionnaire included additional items on severe hypoglycaemia (hospitalisation or unconsciousness), head injury and family history of dementia. The modified Barthel index assessed basic activities of daily living and was supplemented by questions on instrumental activities of daily living (transport, financial affairs, telephone use, control of medication).

A two-step procedure was used for assessment of cognitive function, with initial screening followed by more detailed assessment. The screen utilised sensitive cutoff points to detect early cognitive impairment and was defined by a Mini-Mental State Examination (MMSE) score <28/30 [25] or a score ≥3.1 on the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) [26] or subjective memory loss. The IQCODE is a reliable informant questionnaire that is unaffected by education or language. Research staff with requisite language skills rated non-English versions of the MMSE (Italian in 39 participants, Croatian in four participants and Portuguese in two participants) when necessary.

Participants positive in the screen underwent neuro-cognitive testing (global cognition, premorbid intelligence, memory, language, visuospatial, executive functions; data not presented) and an assessment by clinicians experienced in the diagnosis of cognitive disorders (D. G. Bruce, R. M. Clarnette, O. P. Almeida). The clinical assessment included an informant whenever possible, a standard neurological history and examination (for CVD) and scrutiny of hospital records for supplementary data. Patients with dementia were offered brain magnetic resonance imaging (MRI), and/ or existing recent clinical brain scan (MRI or computed tomography) data were collected where available. A random sample of participants who screened negative (34 participants, 11.3%) underwent the same assessment protocol to check the screening method; none of these participants had cognitive impairment or dementia. Ratings of functional capacity were based on the Clinical Dementia Rating scale [27]. Dementia was diagnosed clinically using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Diagnoses of cognitive impairment without dementia were based on the clinical exclusion of dementia and all had a Clinical Dementia Rating scale rating of 0.5. Dementia subtypes were classified using standard criteria for AD, vascular dementia and dementia with Lewy bodies [28–30]. All cognitive diagnoses were finalised at consensus meetings of the investigators using all available information.

Some participants failed to complete the protocol because of withdrawal or lack of informant ($n=46$). Of these, 26 underwent clinical or neurocognitive assessments and the remaining 20 were judged to be cognitively normal

based on absence of memory complaints, normal MMSE scores (≥27) and supplementary data from hospital records. Of 173 participants who screened positive, all except six underwent a clinical assessment. Two clear-cut cases of dementia were diagnosed without clinical assessment based on available data.

Statistics The computer package SPSS for Windows (version 11.5) was used. Data are presented as proportion, mean±SD, geometric mean (SD range) or (in the case of variables which did not conform to a normal or log-normal distribution) medians and interquartile range (IQR). Where annual values of variables were available, updated means were calculated.

For multiple comparisons of independent samples, the χ^2 test was used for proportions, ANOVA for normally distributed continuous variables, and the Kruskal–Wallis H test for non-normally distributed variables. For two-sample comparisons of proportions we used Fisher's exact test, for normally distributed variables we used Student's t test, and for non-normally distributed variables we used the Mann–Witney U test. Multiple logistic regression analysis using forward conditional modelling ($p<0.05$ for entry and >0.10 for removal) was performed to determine independent associates of cognitive categories. All clinically plausible variables with $p<0.20$ in the respective bivariate analyses were considered for the models.

Results

Sample characteristics and prevalence of cognitive diagnoses The 302 study participants were aged 76.0±4.6 years, 48.3% were male and nine lived in residential care. The duration of clinical diabetes was 11.2 (IQR 8.5–16.5) years, 99.0% had type 2 diabetes, 46.4% had HbA$_{1c}$ levels ≤7 and 36.4% were obese. The duration of follow-up was 7.6± 1.0 years. In comparison with the present sample, the 285 eligible participants who declined participation were older (77.4±6.3 vs 75.0±4.6 years, $p<0.001$), had a longer duration of diabetes [11.9 (IQR 8.6–18.1) vs 10.3 (IQR 7.5–15.4) years, $p<0.001$] and were more likely to die during the recruitment period (23.8 vs 4.3%, $p<0.001$).

Dementia was present in 28 participants (9.3%) and cognitive impairment without dementia in 60 (19.9%). The causes of dementia were probable AD (16 participants), possible AD with stroke (eight participants), probable vascular dementia (three participants) and probable Lewy body dementia (one participant). Neuroradiological data were available in 17 participants (ten with probable AD).

Cross-sectional associations Table 1 summarises the characteristics of patients classified by cognitive status at the

Table 1 Cross-sectional associations at the time of cognitive assessment by cognitive categories (cognitive impairment cases are non-demented)

	Normal (n=214)	Cognitive impairment (n=60)	Dementia (n=28)	p value[c]
Age at assessment	75.1±4.3	76.1±4.6	79.3±5.1[d]	0.001
Sex (% male)	44.4	61.7	50.0	0.053
Type of diabetes (% type 2)	99.1	98.3	100	0.75
Duration diabetes (years)[a]	10.8 (8.3–15.4)	12.1 (8.6–18.1)	13.7 (9.6–21.4)[d]	0.037
Ethnicity (%)				
Anglo-Celt	69.6	71.7	71.4	0.94
Southern European	16.4	23.3	17.9	0.46
Education (% >primary school)	76.9	75.0	71.4	0.80
Not fluent in English (%)	13.6	13.3	17.9	0.82
Diabetic treatment (%)				
Diet	18.2	11.7	17.9	0.48
Oral hypoglycaemic agent	57.3	53.3	46.4	0.50
Insulin (with or without oral hypoglycaemic agent)	24.3	35.0	35.7	0.15
Fasting glucose (mmol/l)[a]	8.0 (6.5–9.7)	8.0 (6.3–9.9)	8.2 (6.6–9.8)	0.96
HbA$_{1c}$ (%)[a]	7.1 (6.5–8.0)	7.2 (6.6–8.3)	7.3 (6.7–8.3)	0.49
BMI (kg/m^2)	28.6±4.7	29.5±4.2	26.6±4.7	0.050
Overweight/obese waist/hip ratio (%)	76.3	71.7	77.3	0.75
Hypoglycaemia, hospitalised (%)	3.8	14.0[e]	16.0[e]	0.004
Systolic BP (mmHg)	151±24	157±22	146±23	0.07
Diastolic BP (mmHg)	75±17	77±15	79±26	0.45
Mean arterial pressure (mmHg)	100±15	104±14	101±19	0.32
BP-lowering medication (%)	82.3	81.0	71.4	0.39
Cholesterol (mmol/l)	4.8±0.9	4.7±0.9	4.8±1.1	0.82
HDL-cholesterol (mmol/l)	1.3±1.0	1.2±0.3	1.3±0.4	0.61
Serum triacylgcerol (mmol/l)[b]	1.5 (0.3–7.5)	1.4 (0.9–2.4)	1.4 (0.8–2.5)	0.57
Lipid-lowering medication (%)	56.7	55.2	25.0[e]	0.007
Albumin:creatinine ratio (mg/mmol)[b]	3.5 (0.8–16.3)	3.0 (0.5–16.0)	8.1 (1.7–39.7)	0.047
Nephropathy (%)	51.0	41.5	70.0	0.09
Neuropathy (%)	30.0	38.3	39.3	0.35
Peripheral arterial disease (%)	37.8	45.0	75.0[e]	0.002
Coronary heart disease (%)	34.3	34.5	53.8	0.14
Cerebrovascular disease (%)	16.0	36.2[e]	42.3[e]	0.001
Depression symptoms (%)	11.3	15.5	17.4	0.53
ApoE ε4 (%)	17.1	20.3	26.9	0.45

Values are means±SD

[a] Values are medians with IQR

[b] Values are geometric means with ranges

[c] p value for tests of multiple comparisons; [d] p<0.05, [e] p<0.01 vs normal in two-sample comparisons (no adjustment for multiple tests)

time of cognitive assessment. Compared with normal participants, patients with dementia were significantly older, had a longer duration of diabetes, and were more likely to have been hospitalised with hypoglycaemia, less likely to take lipid-lowering medication and more likely to have PAD and CVD. Participants with cognitive impairment without dementia were significantly more likely to have been hospitalised with hypoglycaemia and to have CVD. Important non-significant results included education, depression, ApoE status, HbA$_{1c}$ levels, BP, lipid concentrations and CHD. Additional non-significant variables included waist circumference, prior or current antidepressant use, a history of head injury and a family history of dementia (data not presented).

Multiple logistic regression was used to investigate independent associations with cognitive impairment. Four models were explored in which cognitively normal participants (n=214) were compared with each of the following categories: (1) all cognitively impaired participants grouped as a single variable; (2) cognitive impairment without dementia alone with demented participants excluded; (3) all demented participants; and (4) participants with probable AD alone (Table 2). Dementia was independently associated with older age, male sex, diabetes duration and PAD. Probable AD was associated with the same variables with the exception of PAD. Cognitive impairment without dementia was associated with male sex and CVD.

Table 2 Independent cross-sectional associations (odds ratios and 95% CI) comparing non-impaired participants (n=214) with all cognitive impairment, cognitive impairment without dementia alone, all dementia alone and probable Alzheimer's disease alone

	All cognitive impairment (n=88)	Cognitive impairment (n=60)	All dementia (n=28)	Alzheimer's disease (n=16)
Age (per decade)			5.38 (1.73–16.72)[b]	11.11 (2.60–47.51)[b]
Male sex	2.68 (1.45–4.95)[b]	2.40 (1.24–4.67)[b]	5.25 (1.58–17.42)[b]	3.92 (1.02–15.11)[a]
Duration diabetes (increase of 5 years)	1.31 (1.06–1.63)[a]		1.45 (1.03–2.05)[a]	1.50 (1.04–2.14)[a]
Stroke history	3.18 (1.61–6.26)[c]	3.33 (1.63–6.77)[c]		
Peripheral arterial disease	2.03 (1.11–3.73)[a]		4.54 (1.39–14.78)[a]	

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

Table 3 Baseline predictors of cognitive status determined an average 7.6 years prior to cognitive assessment

	Normal (n=214)	Cognitive impairment (n=60)	Dementia (n=28)	p value[c]
Age at baseline (years)	67.8±4.5	68.9±4.7	71.7±4.8[e]	0.001
Duration diabetes (years)[a]	2.8 (0.6–8.0)	4.3 (1.0–10.0)	8.3 (7.0–9.9)	0.06
Diabetic treatment (%)				
Diet	37.9	35.0	32.1	
Oral hypoglycaemic agent	53.7	48.3	46.4	0.17
Insulin (with or without oral hypoglycaemic agent)	8.4	16.7	21.4	
Fasting glucose (mmol/l)[a]	8.2 (6.9–10.5)	8.3 (7.0–9.9)	8.1 (6.7–11.4)	0.97
HbA$_{1c}$ (%)[a]	7.3 (6.4–8.6)	7.5 (6.2–8.6)	7.8 (6.8–9.1)	0.40
Ever experienced hypoglycaemia (%)	24.2	30.0	28.6	0.62
BMI (kg/m^2)	28.9±4.6	29.6±4.2	27.7±4.8	0.20
Overweight/obese waist/hip ratio (%)	76.2	61.7	60.7	0.034
Systolic BP (mmHg)	151±22	154±22	161±22	0.09
Diastolic BP (mmHg)	79±12	79±9	81±12	0.69
Mean arterial pressure (mmHg)	103±13	104±11	108±13	0.23
BP-lowering medication (%)	56.5	56.7	57.1	1.0
Cholesterol (mmol/l)	5.5±1.0	5.1±0.9	5.5±1.0	0.06
HDL-cholesterol (mmol/l)	1.08±0.32	1.06±0.34	1.12±0.32	0.68
Triacylglycerol (mmol/l)[b]	1.9 (1.1–3.2)	1.7 (1.0–3.0)	1.9 (1.3–2.9)	0.62
Lipid-lowering medication (%)	15.0	15.0	7.1	0.53
Albumin:creatinine ratio (mg/mmol)[b]	2.3 (0.8–7.2)	1.9 (0.6–6.3)	3.6 (0.8–16.1)	0.06
Nephropathy (%)	34.1	31.0	50.0	0.20
Retinopathy (%)	13.3	20.3	16.0	0.40
Peripheral neuropathy (%)	26.7	29.6	35.7	0.59
Peripheral arterial disease (%)	21.1	28.8	57.1[e]	0.001
Coronary heart disease (%)	28.8	39.0	42.9	0.15
Cerebrovascular disease (%)	7.0	10.0	25.0[e]	0.008
Depression (%)	21.1	27.1	35.7	0.18
Any exercise in past 2 weeks (%)	82.2	80.0	60.7[d]	0.028
Smoking status (%)				
Never	49.5	36.7	42.9	
Ex-	41.0	53.5	39.3	0.27
Current	9.4	10.0	17.9	
Alcohol (standard drinks/day)[a]	0.1 (0–0.8)	0 (0–0.8)	0 (0–0.3)	0.23

Values are means±SD

[a] Values are medians with IQR

[b] Values are geometric means with ranges

[c] p value for tests of multiple comparisons; [d] $p<0.05$, [e] $p<0.01$ vs normal in two-sample comparisons (no adjustment for multiple tests)

Table 4 Independent longitudinal baseline predictors (odds ratios and 95% CI) of cognitive diagnoses, comparing cognitively normal participants (*n*=214) with all cognitive impairment, cognitive impairment without dementia alone, all dementia alone and probable Alzheimer's disease alone

	All cognitive impairment (*n*=88)	Cognitive impairment (*n*=60)	All dementia (*n*=28)	Alzheimer's disease (*n*=16)
Age (per decade)	2.22 (1.26–3.91)[b]		4.00 (1.59–10.10)[b]	9.95 (3.09–32.07)[c]
Duration diabetes (increase of 5 years)	1.34 (1.11–1.63)[b]		1.69 (1.24–2.32)[b]	1.64 (1.19–2.25)[b]
Peripheral arterial disease	2.23 (1.25–3.99)[b]		5.35 (2.08–13.72)[c]	
Waist/hip ratio (overweight/obese)	0.44 (0.25–0.78)[b]	0.52 (0.28–0.96)[a]	0.21 (0.07–0.61)[b]	
Cholesterol (mmol/l)		0.71 (0.52–0.98)[a]		
Diastolic BP (increase 5 mmHg)				1.32 (1.04–1.69)[a]
Recent exercise			0.26 (0.09–0.73)[a]	

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

Longitudinal predictors In bivariate analyses of baseline variables (Table 3), subjects who later developed dementia were older, more likely to have PAD and CVD and less likely to exercise. No differences were seen between normal participants and those with cognitive impairment without dementia. In addition, there were no differences between normal participants and each of the cognitive categories in updated mean fasting glucose, HbA$_{1c}$, or systolic, diastolic or mean arterial BP (data not shown).

Multiple logistic regression was employed as described in the preceding section (Table 4). Independent longitudinal predictors of dementia were older age, diabetes duration and PAD, while higher waist/hip ratios and taking exercise were protective. AD was predicted by age, diabetes duration and diastolic BP. Cognitive impairment without dementia was predicted by higher waist/hip ratios and higher cholesterol levels (i.e. these variables were protective).

Discussion

In the present study, dementia was evident in almost 10% of the sample, another 20% fulfilling criteria for cognitive impairment without dementia. Applying standard criteria, probable or possible AD was present in 86% of participants with dementia and 39% had a significant cerebrovascular component. These data highlight the high prevalence of cognitive disorders in community-dwelling older people with diabetes.

There were several main findings in relation to risk factors. Both PAD and diabetes duration were independent predictors of dementia in analyses that controlled for a range of potential confounders, including age and previously implicated risk factors, glycaemic control [9, 13], insulin treatment [14, 15] and hypertension [8, 9]. The association between PAD and dementia was strong and participants with PAD had five times the risk of developing dementia.

We carried out the analysis in participants diagnosed with probable AD in order to explore potential relationships in the absence of CVD, although we acknowledge that the small numbers of cases limits the strength of our conclusions. Diabetes duration was independently associated with AD after controlling for confounders and PAD dropped from this model. These findings are consistent with one or more unmeasured diabetes-related factors being involved in the pathogenesis of AD in diabetes over and above CVD and its risk factors. Variables likely to be related to diabetes duration that have been considered possible causes of AD include chronic low-level inflammation, which is associated with atherosclerosis in type 2 diabetes [31], advanced glycation end-products [11], and hyperinsulinaemia and/or insulin resistance [10, 12].

PAD assessed by the ankle/brachial index indicates the presence of severe, diffuse atherosclerosis and PAD has an increased prevalence in diabetes [32]. The present results are consistent with PAD acting as a marker for subclinical cerebrovascular disease since there was an association with dementia but not AD. However, the Cardiovascular Health Study found that a low ankle/brachial index predicted both incident dementia and AD [6]. This disparity may be explained by the small numbers of AD cases limiting statistical power in the present study. Risk factors for PAD in diabetes include hypertension, hyperglycaemia, dyslipidaemia and smoking [23, 33]; hence, atherosclerosis may explain the relationship between cardiovascular risk factors and dementia in diabetes [8, 9]. An important clinical implication is the possibility that the risk of dementia can be reduced by intensive risk factor management.

There were several other findings. The lack of association between ApoE ε4 and cognitive deficits is consistent with recent reports indicating that diabetes may be a more powerful risk factor for AD in ApoE ε4-negative participants [34, 35]. The association with male sex in the present sample may reflect the importance of vascular factors in diabetes, as vascular dementia is more common in men [36]. The finding that baseline diastolic BP predicted AD is consistent with

other studies of mid-life BP [37]. Similarly, the protective effect of baseline exercise is consistent with previous research [38, 39]. It is highly unlikely that central obesity and hypercholesterolaemia protect against dementia [40]; the findings of this study in relation to these factors are probably explained by the participants with dementia having already lost body fat when assessed at baseline, as loss of fat stores is known to occur years before the onset of dementia [40].

The risk factor profile for cognitive impairment without dementia differed from that for dementia, and incident CVD was associated with the former but not the latter. Cognitive impairment without dementia, as defined in the present study, is a broad classification [41] with a high prevalence in diabetes [42]. Mild cognitive impairment is a more restrictive category with a high rate of transition to dementia, but it has recently been shown that the subgroup of mild cognitive impairment associated with CVD is less likely to progress to dementia [43]. Follow-up studies will be required to determine whether these patients will progress to dementia.

The present study has strengths and limitations in addition to those discussed above. The main strengths are the representative nature of the FDS and the comprehensive nature of the diagnostic procedure for cognitive impairment, potential risk factors and possible confounders. The major limitations relate to the cohort study design, with its inherent tendency for recruitment and survivor bias. There was considerable attrition from the FDS; this left a study sample that was relatively healthy but resulted in a fairly small sample with relatively few cases of dementia. Because of the healthy nature of the sample, the variables of interest, cognitive impairment and CVD, were likely to be under-represented in the sample. Conclusions from our study, particularly in relation to the participants with AD, need to be drawn with a degree of caution because of small numbers. The study was longitudinal but cognition was not assessed at baseline. Thus we cannot exclude the possibility that participants had dementia at recruitment, which limits the predictive value of the prospective models. Finally, we studied a cohort of diabetic participants and the lack of a non-diabetic comparison group limits potential conclusions to diabetic populations.

PAD is a potent, modifiable risk factor, indicating that atherosclerosis, either directly or indirectly, contributes to the risk of dementia in diabetes. The finding that the duration of diabetes is an independent risk factor for dementia and AD lends support to existing hypotheses that invoke insulin-related factors or the accumulation of advanced glycation end-products in the development of dementia in older diabetic patients.

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