Risk of dementia in diabetes mellitus: a systematic review

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The relation between diabetes and major types of dementia is controversial. This systematic review examines the incidence of dementia in people with diabetes mellitus. We identified 14 eligible longitudinal population-based studies of variable methodological quality. The incidence of "any dementia" was higher in individuals with diabetes than in those without diabetes in seven of ten studies reporting this aggregate outcome. This high risk included both Alzheimer's disease and vascular dementia (eight of 13 studies and six of nine studies respectively). Detailed data on modulating and mediating effects of glycaemic control, microvascular complications, and comorbidity (eg, hypertension and stroke) were generally absent. The findings of mechanistic studies suggest that vascular disease and alterations in glucose, insulin, and amyloid metabolism underlie the pathophysiology, but which of these mechanisms are clinically relevant is unclear. Further high quality studies need to be initiated, with objective diabetes assessment, together with reliable methods to establish the contribution of vascular disease and other comorbidity to dementia.

Introduction

Diabetes mellitus is associated with changes in cognition. In type 1 diabetes mellitus this association is shown by a mild to moderate slowing of mental speed and a diminished mental flexibility.[1] In type 2 diabetes cognitive changes mainly affect learning and memory, mental flexibility, and mental speed.[2–4] Several large longitudinal population-based studies have shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes.[5] The determinants of this accelerated cognitive decline, however, are less clear;[5] some researchers suggest that hypertension could be an important mediator,[6] whereas others have found associations with glycaemic control.[7]

Although the association between diabetes and these modest changes in cognition is now well established, the relation between diabetes and dementia is an area of controversy. Early studies that reported a low rate of diabetes in patients with Alzheimer's disease,[8–10] suggested that diabetes and Alzheimer's disease might not coexist.[9] However, a more recent study suggested that type 2 diabetes or impaired fasting glucose might be present in up to 80% of patients with Alzheimer's disease.[11] These opposing results clearly indicate that studies of the prevalence of diabetes in people with established dementia are unlikely to provide reliable data for the risk of dementia in individuals with diabetes. These differing outcomes may be the result of methodological issues, such as survival bias of non-diabetic patients with Alzheimer's disease and the possible effects of Alzheimer's disease itself on glucose metabolism,[12] which might obscure the relation with diabetes in more advanced cases of dementia. Population-based studies that compare the incidence of dementia between patients with and without diabetes provide more reliable risk estimates than studies on patients with established dementia.

Both the absolute and relative numbers of elderly people who are affected by diabetes are expected to increase over the next few decades.[13] Better insight into the strength and the nature of the association between diabetes and dementia is therefore of great importance.

In this article, we systematically review studies on the incidence of dementia in patients with diabetes mellitus to determine the strength of the association between diabetes and dementia. We also examined the extent to which researchers investigated potential modulators and mediators of the risk of dementia in people with diabetes. We discuss underlying mechanisms and relevant neuropathological and neuroradiological studies.

Methods

Identification of studies

Studies were identified by searches of MEDLINE (1966 to August, 2005) and EMBASE (1966 to August, 2005) with the search terms "diabet* AND Alzheim* OR dement*". Searches were restricted to papers published in English and the Embase search was restricted to "human studies". The bibliographies of relevant original and review articles were screened. This systematic review aimed to include all published studies that provide an estimate of the incidence of dementia among patients with diabetes mellitus in the general population. For inclusion into the systematic review, papers therefore had to meet the following criteria: the study cohort was recruited at the population level (ie, not hospital based); the study had a longitudinal design; the incidence of Alzheimer's disease, mixed dementia, or vascular dementia could be compared between patients with and without diabetes. Studies on people with cognitive impairments but not dementia were excluded, as were studies of the prevalence of diabetes in patients with established dementia. The titles and abstracts of all articles identified by the search were screened and potentially relevant articles were retrieved and assessed according to the criteria. Additional relevant articles for the discussion on methodological issues, potential risk factors, and underlying mechanisms were identified through MEDLINE.

Results of the search

The MEDLINE search yielded 1195 hits, the EMBASE search yielded 1826 hits. Screening of titles and abstracts identified 43 potentially relevant papers, including 14 reviews, which were retrieved for screening of the

bibliographies. 20 papers, covering 14 different study populations met the inclusion criteria and went forward to the data extraction stage.[14–33]

When more than one paper reported on the same population,[19,20,22,23,28,30–33] the paper with the largest population sample and the most detailed information about diabetes was included.[30–33] There were two exceptions. First, two papers were included from the Washington Heights-Inwood Columbia Aging Project because one paper included data on vascular dementia[20] whereas the other provided more detailed data for Alzheimer's disease.[28] Second, two papers were included from the Honolulu-Asia Aging Study, one of which reported the incidence of dementia 25 years after midlife diabetes assessment,[19] the other reporting incident dementia at age 80 years, after diabetes assessment at age 77 years.[22] Hence, the data from 16 papers, covering 14 study populations, are addressed in this review (table 1).

Quality assessment

The quality of reporting of all included studies was appraised with checklists developed for longitudinal observational study designs.[34,35] These checklists included external validity (recruitment, participation at follow-up), internal validity (duration of follow-up, assessment of exposure, outcome status and covariates, analytical approach), and descriptive issues. Assessment of quality was based on criteria developed by two of the authors (CB, EB), according to these published checklists.[34,35] EB and CB independently evaluated each of the included studies according to these criteria (panel).

***Panel:* Quality assessment of studies**

Population selection and recruitment (maximum 2 points)
- Well-defined population sample (1 point)
- Baseline response rate 70% or more (1 point)

Participation at follow-up (maximum 2 points)
- Participation rate at follow-up 60–69·9% (1 point),

or
- 70% response or more (2 points)

Diabetes assessment (maximum 2 points)
- Diabetes status based on medical records (0 points),

or
- random glucose measurement (1 point),

or
- fasting glucose/oral glucose tolerance test (2 points)

Dementia assessment and diagnosis (maximum 2 points)
- Based on medical records (0 points),

or
- active screening with ad-hoc criteria (1 point),

or
- on recognised international criteria by a central consensus committee (2 points)

Data analysis (maximum 2 points)
- Analysis excluded those with dementia at baseline, and included adjustment for confounders (1 point)
- Prospective analysis with estimation of standard error taking design features into account (1 point)

Results

Study populations

The 14 study populations included participants of different ethnic origins: white, Hispanic, black, and, Asian. Further demographic details are presented in table 1. Most studies included both individuals living in institutions and those living at home in their baseline study sample. Recruitment varied among the studies from sampling within religious orders to true population sampling. The Rochester sample simply

	Country	Follow-up (years)	Patients base/ FU*	Patients with diabetes*	Age baseline	Gender (% men)	Quality rating†
Katzman 1989[14]	USA	3·7	488/397	ND/46	79	36	5
Yoshitake 1995[15]	Japan	7	828‡	70/ND	74	40	7
Leibson 1997[16]	USA	6·9	~75 000	ND/1455	..	..	6
Brayne 1998[17]	UK	2·4	461/376	ND/25	84	36	7
Ott 1999[18]	Netherlands	2·1	6370‡	692/ND	69	39	9
Curb 1999[19]	USA (Hawaii)	25	8006/3734	ND/259	53	100	5
Luchsinger 2001[20]	USA	4·3	1799/1262	229/255	76	31	6
Hassing 2002[21]	Sweden	6	702‡	ND/108	84	34	4
Peila 2002[22]	USA (Hawaii)	2·9	3508/2574	ND/900	77	100	7
MacKnight 2002[23]	Canada	5	9131/5574	ND/503	74	39	7
Yamada 2003[24]	Japan	30	ND/1774	ND/ND	43	27	7
Arvanitakis 2004[25]	USA	5·5	847/824	91/127	75	31	6
Schnaider Beeri 2004[26]	Israel	35	10 059/1892	825/42	45	100	7
Xu 2004[27]	Sweden	4·7	1301‡	114/ND	81	25	7
Luchsinger 2005[28]	USA	5·5	1786/1138	313/231	76	32	6
Whitmer 2005[29]	USA	~35	ND/8845	ND/1004	42	46	5

*Data are number of patients at baseline/number of patients at follow up; †all studies were rated for methodological quality (see methods section), the maximum score that could be obtained was 10; ‡studies that actively pursued the occurrence of dementia in individuals who did not attend follow-up, for example by checking medical records. ND=not determined.

***Table 1:* Population characteristics in studies of dementia and diabetes mellitus**

	Reference	Quality rating	Results (95% CI)	Additional adjustment for vascular risk factors
Any dementia	Ott[18]	9	1·9 (1·3–2·8)	
	Brayne[17]	7	OR 2·6 (0·9–7·8)	
	Peila[22]	7	1·5 (1·0–2·2)	1·5 (1·0–2·2)
	MacKnight[23]	7	1·2 (0·9–1·7)	1·3 (0·9–1·8)
	Xu[27]	7	HR 1·5 (1·1–2·1)	HR 1·5 (1·0–2·1)
	Leibson[16]	6	SMR 1·6 (1·3–2·0)	
	Hassing[21]	4		1·2 (0·8–1·7)
Alzheimer's disease	Ott[18]	9	1·9 (1·2–3·1)	
	Brayne[17]	7	OR 1·4 (1·1–17·0)	
	Yoshitake[25]	7	2·2 (1·0–4·9)	
	Peila[22]	7	1·7 (1·0–2·8)	1·8 (1·1–2·9)
	MacKnight[23]	7	1·2 (0·8–1·8)	1·3 (0·8–2·0)
	Xu[27]	7	HR 1·3 (0·8–1·9)	HR 1·3 (0·9–2·1)
	Leibson[16]	6	SMR 1·6 (1·3–2·0)	
	Luchsinger[28]	6	HR 2·4 (1·8–3·2)	HR 2·0 (1·4–2·9)
	Arvanitakis[25]	6	HR 1·7 (1·1–2·5)	
	Katzman[14]	5	OR 0·5 (0·1–2·3)	
	Hassing[21]	4		0·8 (0·5–1·5)
Vascular dementia	Ott[18]	9	2·0 (0·7–5·6)	
	Yoshitake[25]	7	2·8 (2·6–3·0)	
	Peila[22]	7	2·2 (1·1–4·7)	2·3 (1·1–5·0)
	MacKnight[23]	7	2·2 (1·3–3·6)	2·0 (1·2–3·6)
	Xu[27]	7	HR 2·2 (1·1–5·0)	HR 2·6 (1·2–6·1)
	Luchsinger[20]	6	HR 4·2 (2·2–8·3)	HR 3·4 (1·7–6·9)
	Hassing[21]	4		2·5 (1·4–4·8)

Risk of dementia in people with diabetes relative to those without diabetes. Results were adjusted for age and sex (except the Katzman study), mostly for education, and vascular risk factors (eg, history of stroke, hypertension, and heart disease). Diagnoses were made using DSM III[40] (dementias), NINCDS-ADRDA[42] (Alzheimer's disease), and NINCDS-AIREN[43] or California criteria[47] (vascular dementia). All results are expressed as relative risks unless otherwise stated. OR=odds ratio; HR=hazard ratio; SMR=standard morbidity ratio.

***Table 2*: Risk of incident dementia in patients with diabetes mellitus—longitudinal studies with late-life assessment**

used the population denominator and the medical records associated with that population, with no discussion of in and out migration.[16] The number of drop-outs during follow-up was specified in all but four studies,[16,19,24,29] but only one study provided a clear consort-style audit trail of their respondents.[26] In most studies data for possible incident cases of dementia among drop-outs were absent. Some researchers did seek information about dropouts;[15,18,21,27] however, dementia is known to be poorly documented in routine records. Drop-outs were generally not specified according to diabetes status. The possible implications of dropouts and non-responders in longitudinal studies in elderly people have been reviewed elsewhere.[36]

Assessment of diabetes

Both the method and timing of diabetes assessment affect risk estimates of dementia in people with diabetes. The methods used to identify previously undiagnosed cases of diabetes varied across studies, including random measurements of blood glucose concentrations,[27,29] or fasting blood glucose concentrations combined with an oral glucose tolerance test.[18,19,22,24,26] Eight studies defined diabetes solely on the basis of medical history or medication use, or did not assess blood glucose concentrations in all participants.[14–17,20,21,23,25] Because diabetes is commonly (around 30%)[37,38] undiagnosed in elderly people, in these latter studies a substantial proportion of the people with diabetes might have been erroneously assigned to the non-diabetic group. Similarly, longitudinal studies that assess diabetes only at baseline[14,15,18,19,22–24,26,27,29] will have missed incident cases of diabetes. As the annual incidence of diabetes increases with age (0·3–0·5% in people age 50–60 years, 0·5–1·0% for 60–70 years, and 1% above 70 years)[39] this change will particularly affect studies with an elderly population or with a long follow-up. The inclusion of undiagnosed individuals with diabetes in the non-diabetic group will lead to an underestimation of the risk attributable to diabetes. The size of this effect, however, will be modest because the proportion of undiagnosed people with diabetes in the total non-diabetic group will still be small. Indeed, the risk of dementia in studies that screened actively for diabetes is largely similar to those that did not (tables 1 and 2). The studies did not distinguish between type 1 and type 2 diabetes, but in view of the age of the populations involved, most participants probably have type 2 diabetes.

Assessment of dementia

All but five[16,19,24,26,29] of the studies assessed dementia at baseline and follow-up. In four of these studies,[19,24,26,29] however, the baseline assessment was at mid-life, when dementia is very uncommon. Three studies based the diagnosis of dementia on the medical records of participants.[16,21,29] In the remaining studies patients with dementia were generally identified by an initial screening across the whole study population, then by a more detailed diagnostic work-up in patients suspected of cognitive impairment. The nature of this work-up varied, but always included a standard interview, an examination by a neurologist, psychiatrist, or a geriatrician; and, in most cases, a standard neuropsychological examination. A few studies obtained brain imaging from all participants,[14,15,19,22] whereas in other studies imaging was added if needed on clinical grounds.[20,23,25] In most studies diagnosis of dementia was then established by a consensus committee.[14,18–24,27]

The diagnostic criteria applied were similar across studies, which is probably because of the narrow time frame (1995–2005) in which all but one study[14] were published. Any dementia was generally defined according to the critera from the *Diagnostic and Statistical Manual of Mental Disorders, third edition*[40] or the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM IV).[41] Alzheimer's disease was diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[42] including both cases of probable and possible Alzheimer's disease. Vascular dementia was mostly diagnosed according to

the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN) criteria,[43] including both probable and possible cases. The reliability of these clinical diagnostic criteria is a source of ongoing debate. Previous studies have tried to measure sensitivity and specificity with neuropathology as a gold standard.[44] Against this standard a diagnosis of probable Alzheimer's disease based on the NINCDS-ADRDA workgroup criteria has a fair sensitivity (49–100%) and specificity (47–100%), whereas a diagnosis of possible Alzheimer's disease has even better sensitivity (85–96%), at the cost of specificity (32–61%).[44] For a clinical diagnosis of vascular dementia according to the NINDS-AIREN criteria specificity is high (93–98%), but sensitivity is low (20–43%).[44–46] However, such results come from specialist research settings rather than population-based studies.

Within individual studies the reliability of these diagnostic criteria will be affected by the nature of the diagnostic work-up. A detailed standard work-up including imaging and a consensus-based diagnosis, with strict adherence to the criteria, will obviously increase the reliability. Nevertheless, even in a research setting, patients can be misdiagnosed. This possibility of misdiagnosis must be noted, especially when considering data from studies that distinguish between Alzheimer's disease and vascular dementia, the boundaries of which remain controversial. We therefore did not focus this review on dementia subtype issues.

Strength of the association

Four studies assessed diabetes at mid-life (before age 60 years), and incident dementia at advanced age (age 70–80 years;[19,24,26,29] table 3). In the remaining studies both baseline and follow-up assessments were done in patients older than age 65 years (table 2[47]).

Three of the studies, in which midlife diabetes was assessed, reported an increased risk of dementia in people with diabetes when dementia was assessed after an extended follow-up of 25–35 years. The incidence of any dementia was increased in individuals with diabetes in two of three studies reporting this aggregate outcome. The two studies that assessed the incidence of Alzheimer's disease had apparently opposing results.[19,24] In the Japanese Adult Health Study there was a substantial increase in the odds of developing Alzheimer's disease,[24] whereas the Honolulu-Asia Aging Study reported no such effect.[19] However, this latter study was the only study out of four that did not find an association between midlife diabetes and any of the dementia outcome measures. Moreover, later follow-up surveys in the Honolulu-Asia Aging Study recorded a relation between late-life diabetes and dementia.[22] Nevertheless, the findings of these studies on the effects of midlife diabetes need to be interpreted with some caution, because of the long interval between assessment for diabetes and assessment for dementia. Design issues, such as selective survival and incident diabetes during follow-up, can have substantial effects; this is clearly shown in the study by Schnaider Beeri and colleagues,[26] who present comprehensive data on dropout rates. They show that follow-up data were obtained for only 5% of the people with diabetes at baseline and for 20% of the people without diabetes. The high drop-out rate was mostly due to death before the follow-up assessment, an effect that was stronger in the diabetic group, as might be expected.[39] Moreover, in the population from which follow-up data was obtained, the proportion of people with diabetes was 2·2%, which is well below the expected prevalence in this age group.

Outcome measure	Reference	Quality rating	Results (95% CI)
Any dementia*	Schnaider Beeri[26]	7	OR 2·8 (1·4–5·7)
	Curb[19]	5	RR 1·1 (0·7–1·8)
	Whitmer[29]	5	HR 1·5 (1·2–1·8)
Alzheimer's disease	Yamada[24]†	7	OR 4·4 (p<0·01)
	Curb[19]‡	5	RR 1·0 (0·5-2·0)
Vascular dementia	Yamada[24]†	7	OR 1·3 (p=0·06)
	Curb[19]§	5	RR 1·5 (0·8–2·8)

Risk of dementia in people with diabetes relative to those without diabetes. Results were adjusted for age, sex, and education, and in one study,[26] also for vascular risk factors. Diagnostic criteria for dementia: *DSM III[40] or DSM IV;[41] †DSM IV; ‡NINCDS-ADRDA;[42] §California criteria.[47] OR=odds ratio; HR=hazard ratio; RR=relative risk.

***Table 3:* Risk of incident dementia in patients with diabetes mellitus—studies with midlife diabetes assessment**

The longitudinal studies in which both diabetes and dementia were assessed in late life show a fairly consistent pattern (table 2). The incidence of any dementia was increased in people with diabetes in five of seven studies reporting this aggregate outcome. Overall, the incidence of dementia was increased by 50–100% relative to people without diabetes. This increased risk included both Alzheimer's disease and vascular dementia (seven of 11 studies and six of seven studies respectively), with an increase in risk of Alzheimer's disease of 50–100%, and an increase in risk of vascular dementia of 100–150%.

There was no obvious relation between the estimated risk of dementia in patients with diabetes in individual studies and the quality rating that was assigned (table 2), except that the two studies that received the lowest quality ratings presented the lowest estimates of the risk of any dementia and Alzheimer's disease.[14,21] A formal meta-analysis of the dementia-risk estimates from the different studies was not done because of the substantial differences between studies in methodological quality, population size and age, and duration of follow-up.

Confounding, modulating, and mediating factors

Diabetes mellitus is a complex metabolic disorder that is closely associated with other risk factors for accelerated cognitive decline and dementia, such as hypertension and atherosclerotic vascular disease. These risk factors,

together with demographic and socioeconomic factors, diabetes-specific conditions and drugs, other comorbidities (eg, depression), and genetic factors could be important determinants of the increased risk of dementia in people with diabetes.[3,4]

Most of the studies that were included in this systematic review adjusted the risk of dementia in people with diabetes for the potential confounding effects of age and sex. Most studies did not assess premorbid intelligence quotient in their study populations, but did adjust the relative risk estimates for the possible confounding effects of education. Only two studies presented the age-adjusted risk of dementia for men and women with diabetes separately,[16,18] one showing an equal risk for both sexes,[18] one showing a slightly increased risk in men.[16] Across the studies, the ethnic origin of the study populations was different. None of the studies presented data for the relation between ethnic origin and the risk of dementia in people with diabetes. Nevertheless, comparisons of the relative risk of dementia across the different study populations, as presented in tables 2 and 3, do not point towards major effects of ethnic background.

The included studies generally did not provide an in depth analysis of the modulating effect of comorbid disorders, although the effects of publication bias in relation to negative findings are unknown and could affect interpretation. Stroke, vascular disease, and hypertension are known risk factors for dementia in the general population[48,49] and should therefore be taken into account when the relation between diabetes and dementia is examined. Several studies included in this systematic review did provide exploratory analyses into the modulating effects of hypertension and vascular disease. In the Kungsholmen study,[27] the underlying mechanisms of diabetes and hypertension interacted (systolic blood pressure ⩾180 mm Hg) to affect the relative risks of any dementia, Alzheimer's disease, and in particular vascular dementia. By contrast, two other studies reported that adjustment of the relative risk of dementia in diabetic patients for hypertension and other vascular risk factors seemed to have no effect (table 2[22,23]). This finding again concerned the relative risks of any dementia, Alzheimer's disease, and vascular dementia. Notably, in additional analyses from the Kungsholmen study, in which systolic blood pressure was entered together with other vascular risk factors in a multiadjusted model, similar to these two other studies,[22,23] there was no effect of hypertension (table 2).[27] In a paper from the Washington Heights-Inwood Columbia Aging Project,[28] hazard ratios, adjusted for demographics and apolipoprotein E (APOE) status, were presented separately for patients with diabetes, hypertension, or both disorders. The risk of Alzheimer's disease was highest in participants with diabetes only, and the interaction term between diabetes and hypertension indicated that the risk of Alzheimer's disease in individuals with diabetes was lower in the presence of hypertension. There is similar controversy surrounding the relation between diabetes and hypertension in studies on cognitive changes in individuals without dementia; some studies suggest that hypertension is an important mediator,[6] whereas other studies showed that the effect of diabetes on cognition was independent of blood pressure.[7] The operational definition of hypertension and the method of statistical analysis play an essential part, and this issue needs further scrutiny.

The potential mediating effects of diabetes-related factors were also not examined in detail. This may be because most studies that are included in this review were not specifically designed to assess the effects of diabetes on the risk of dementia, but rather aimed to identify risk factors for dementia in elderly people in a broader sense. Therefore, data for diabetes-specific features such as diabetes duration, haemoglobin A_{1C} (HbA_{1c}), and microvascular complications were generally not obtained. Only one study assessed the effect of diabetes duration on the risk of dementia, and observed no effect.[16] However, two other studies showed that screening identified cases of diabetes—which presumably have a shorter or less severe exposure to hyperglycaemia—had a lower risk of dementia than people with a known history of diabetes.[18,22] Diabetes treatment might also be a relevant factor. Data from the Rotterdam study and the Washington Heights-Inwood Columbia Aging Project indicate that the risk of dementia is highest in people with diabetes treated with insulin.[18,20] Whether these results show the severity of diabetes, or an effect of insulin treatment itself, is unknown.

Genetic predisposition could also have a modulating role in the association between diabetes and dementia, but thus far only the involvement of the APOE genotype has been examined. One study adjusted the risk of dementia in people with diabetes for the APOE genotype,[28] whereas two other studies presented the risk of dementia in individuals with diabetes according to the APOE genotype.[22,27] These latter two studies showed that people with diabetes who were carrying the *APOE* ϵ4 allele had a doubled relative risk of dementia compared with patients with either of these risk factors in isolation.[22,27]

Discussion

This systematic review of population-based studies brings together the evidence that the risk of dementia is, in general, increased in patients with diabetes mellitus. This increased risk seems to include both Alzheimer's disease and vascular dementia—although the limitations of clinical diagnostic criteria in the classification of dementia by pathological subtype should be considered, especially in a complex disorder such as diabetes. Therefore, rather than focusing the

discussion on which subtypes of dementia are associated with diabetes, it might be more pragmatic to try and identify which diabetes-related factors, or comorbid conditions, primarily drive the association between diabetes and dementia. Unfortunately, the available epidemiological data lack sufficient detail to reliably identify these factors. In this section, we review neuropathological and neuroimaging data, as well as mechanistic studies, which could provide clues as to which factors should be given consideration in the design of future prospective studies on the relation between diabetes and dementia.

Structural brain abnormalities

In autopsy series, macroscopic brain infarcts are more common in people with diabetes than in people without the disorder.[22,50] Additionally, diabetes is associated with pathological changes in the cerebral microvasculature, including amyloid angiopathy,[22] and capillary basement membrane thickening.[51] Several studies have also examined the incidence of Alzheimer's type pathology in the brains of people with diabetes.[11,22,52,53] An initial report on an autopsy series of patients without dementia indicated that diabetes was not associated with increased Alzheimer's type pathology.[52] However, in this study the overall severity of the pathological changes in both the people with and without diabetes was slight (average Braak stage I),[54] consistent with their not having dementia. A more recent study on brain autopsies of nursing home residents indicated that Alzheimer's type pathology might be less common in people with diabetes than those without diabetes.[53] In the autopsy population from the Honolulu-Asia Aging Study the occurrence of neurofibrillary tangles and amyloid plaques in the hippocampus and cortex in people without the *APOE ϵ4* allele was similar in those with and without diabetes.[22] In *APOE ϵ4* allele carriers, however, these lesions seemed to be more common in people with diabetes than in people without diabetes.[22] In a smaller autopsy study that included patients with and without dementia, a trend towards increased incidence of amyloid plaques in diabetic participants was reported, which correlated significantly with the duration of diabetes.[11]

Neuroimaging studies also shed light on the nature of the structural cerebral changes that occur in association with diabetes. Population-based studies indicate that diabetes is a risk factor for silent and symptomatic brain infarcts seen with MRI.[55,56] Moreover, diabetes is associated with a slight degree of cortical and subcortical atrophy.[57–59] In the early stages of Alzheimer's disease, MRI shows that atrophy is predominantly evident in the medial temporal lobe,[60] whereas atrophy in diabetes is more generalised—not unlike the pattern observed in normal ageing. Thus far, the relation between diabetes and white-matter changes on MRI is less clear.[58,61] This issue needs further attention, because changes in white matter are associated with vascular risk factors and cognitive decline in elderly people[60,62] and might have a mediating role in the risk of dementia in people with diabetes.

Underlying mechanisms

There are many pathophysiological mechanisms through which diabetes might affect the initiation and promotion of the many underlying pathologies associated with dementia.[63] These mechanisms include those which are common to both Alzheimer's disease and vascular dementia, as well as ageing itself. It is increasingly recognised that the brains of people with dementia, particularly in the very old, are likely to show a mixture of pathologies, particularly Alzheimer type and vascular changes.[64] Figure 1 presents a simplified scheme, in which some of the endocrinological, metabolic, and vascular abnormalities that are associated with diabetes and can lead to these different pathologies are indicated. These combined mechanisms can lead to mixed pathology. In some people with diabetes vascular damage will predominate, leading to a form of dementia that will be clinically classified as "pure vascular dementia". In other patients amyloid-related mechanisms may predominate leading to a clinical picture of "pure Alzheimer's disease". Most patients will present with intermediates between these two dementia syndromes.

Ischaemic cerebrovascular disease

Stroke and vascular comorbidity are likely to be important determinants of the risk of dementia in individuals with diabetes. Diabetes is a known risk factor for stroke.[65,66] This risk might not only be attributable to diabetes,[66] but also to associated risk factors for vascular disease. Type 2 diabetes, by far the most common form of diabetes in elderly people, develops in the context of a cluster of these risk factors, including obesity, insulin resistance, atherogenic dyslipidaemia (raised triglyceride concentrations, small LDL particles, and low concentrations of HDL cholesterol), hypertension, and prothrombotic and proinflammatory states. Together these factors constitute the metabolic syndrome, or insulin resistance syndrome.[67,68] Several factors from the metabolic syndrome might be predictors of cerebrovascular disease, ischaemic stroke, and accelerated cognitive decline and dementia.[29,69–73] The combination of these risk factors in the metabolic syndrome and type 2 diabetes might reinforce these effects. Additionally, chronic exposure to hyperglycaemia in diabetes might lead to abnormalities in cerebral capillaries, such as basement membrane thickening.[63,74] These microvascular changes might also lead to chronic and insidious ischaemia of the brain.

Glucose toxicity

Several lines of evidence suggest that "toxic" effects of hyperglycaemia can lead to slowly progressive functional

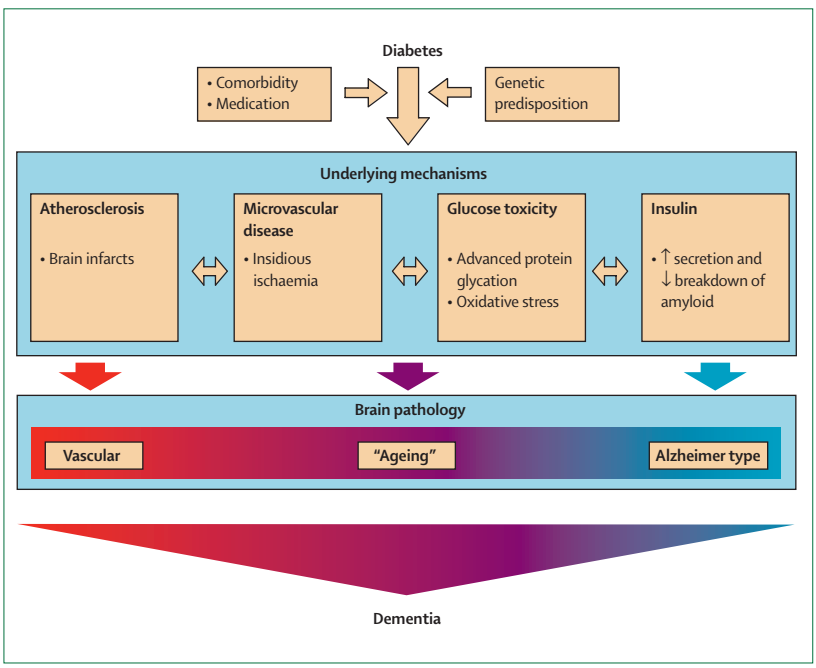

Figure 1: **Proposed pathophysiological mechanisms linking diabetes to changes in the brain and dementia**
Diabetes and its comorbid conditions are associated with an increased risk of atherosclerosis and stroke, leading to vascular pathology in the brain. Glucose-mediated toxicity can lead to microvascular abnormalities and more widespread changes in cognition and brain structure, referred to as accelerated brain ageing. Additionally diabetes and its treatment might interfere with amyloid metabolism, giving rise to Alzheimer's type pathology.

and structural abnormalities in the brain.[63] Chronic hyperglycaemia could thus be one of the determinants of cognitive changes in people with diabetes.[3,4] Rodents with chronic hyperglycaemia express cognitive impairments and abnormalities in synaptic plasticity.[75] Toxic effects of high glucose concentrations are mediated through an increased flux of glucose through the polyol and hexosamine pathways, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavenging of reactive oxygen species, and by advanced glycation of important functional and structural proteins.[76] These processes can affect brain tissue directly, but can also lead to microvascular changes.[63] So, unlike causing circumscript vascular lesions, diabetes might evoke more generalised and widespread microvascular changes in the brain by this process, causing microinfarcts, probably leading to generalised atrophy and white-matter changes. The occurrence of microinfarcts and their relation to brain atrophy and cognitive decline in elderly people is an evolving concept in the area of dementia research.[77,78]

These global-glucose mediated effects on cognition and brain structure might be referred to as "accelerated brain ageing". Although this term is rather non-specific, it might have importance from a conceptual point of view. Several of the above mechanisms that mediate the toxic effects of hyperglycaemia, such as oxidative stress, the accumulation of advanced glycation end-products, and microvascular pathology, are also implicated in the ageing process of the brain.[74,79,80] In fact, the pattern of cognitive changes and brain atrophy in patients with diabetes without dementia mimics certain aspects of brain ageing.[59,74] Although this glucose-mediated "accelerated brain ageing" in diabetes is unlikely to lead to frank dementia in itself, it could certainly reduce the threshold for dementia in combination with other pathological changes.

Changes in insulin and amyloid metabolism

Insulin resistance, at least in the early stages of type 2 diabetes, is associated with compensatory hyperinsulinaemia. Several studies have identified hyperinsulinaemia as a risk factor for accelerated cognitive decline[71] and dementia.[32,69] Part of this association is likely to be mediated through vascular disease because insulin has vasoactive effects.[81] Several population-based studies in participants without diabetes have reported an increased risk of stroke in those with the highest insulin concentrations, an effect that persisted after adjustment for associated other vascular risk factors from the metabolic syndrome.[73] Additionally, insulin might have direct effects on the brain (figure 2).[82,83,84] Insulin is transported actively across the blood–brain barrier,[85] and might even be produced locally in the brain.[86] Insulin receptors are distributed throughout the brain, with particular abundance in the hippocampus and the cortex.[87] Within the brain, insulin is a modulator of food intake and energy homoeostasis,[88] and could also be associated with learning and memory.[89] Ageing is associated with changes in insulin and its receptor in the brain, and these changes might be even more pronounced in patients with Alzheimer's disease.[86,90,91] The observation that activation of the insulin receptor was impaired in brain autopsy samples of patients, has given rise to the notion that Alzheimer's disease could be qualified as "an insulin resistant brain state".[90]

Alterations in insulin and glucose homoeostasis could also affect amyloid metabolism by changes in the brain of insulin and its receptor (figure 2)[92] and by the formation of advanced glycation end-products.[79] The relation between insulin and the metabolism of amyloid-β peptide (Aβ) and tau in particular has been receiving increasing attention over the past few years.[92,93] Aβ is derived from the amyloid precursor protein. After secretion into the extracellular space Aβ can aggregate with other proteins to form senile plaques. Alternatively, excessive Aβ can be cleared through LDL-receptor-related protein-mediated endocytosis, or through direct extracellular proteolytic degradation.[83] This latter process involves insulin-degrading enzyme.[84] Insulin seems to stimulate Aβ secretion and inhibit the extracellular degradation of Aβ by competition for insulin-degrading enzyme.[93] It is tempting to suggest that hyperinsulinaemia in people with type 2 diabetes might

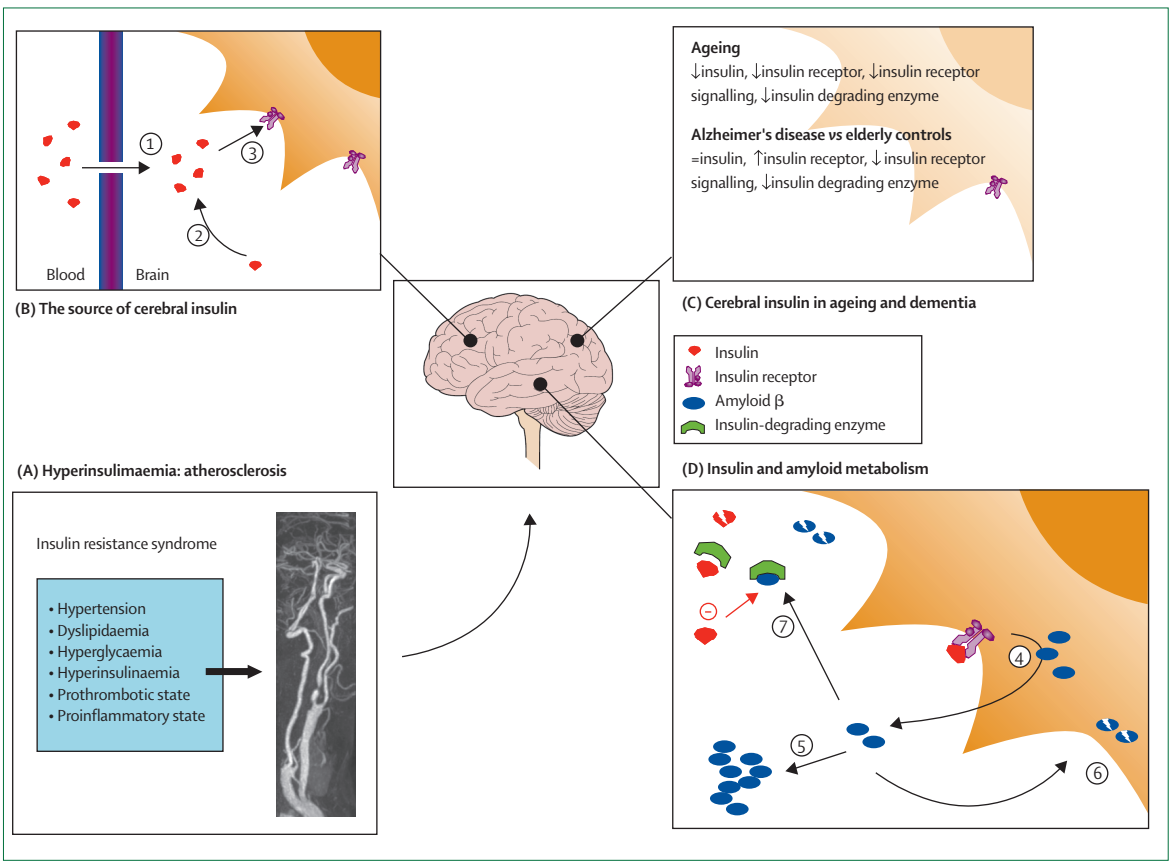

Figure 2: **The potential role of insulin in the pathogenesis of dementia**
Hyperinsulinaemia has been identified as a risk factor for accelerated cognitive decline and dementia, which may be mediated through vascular effects and direct effects of insulin on the brain. Hyperinsulinaemia, in the context of the insulin resistance syndrome, is a risk factor for artherosclerosis (A). Insulin is transported actively across the blood–brain barrier (1), may be produced locally in the brain (2), and—acting through cerebral insulin receptors (3)—modulates food-intake and energy homoeostasis (B).[82] Ageing is associated with changes in insulin and its receptor in the brain, and these changes may be even more pronounced in individuals with Alzheimer's disease(C). Insulin also affects amyloid metabolism (D). Insulin stimulates the secretion of amyloid β (4) into the extracellular space where it can aggregate with other proteins to form senile plaques (5). Alternatively, excessive amyloid β can be cleared through endocytosis (6), or through direct extracellular proteolytic degradation by insulin-degrading enzyme (7).[83,84]

interfere with Aβ metabolism by stimulating its secretion and inhibiting its breakdown,[92,93] but how type 2 diabetes and its treatment affect insulin signaling in the brain is not known, and these suggestions will need to be verified by clinical observations. Nevertheless, recent histopathological data lend support to the potential clinical relevance of these processes. In patients with Alzheimer's disease, insulin-degrading enzyme expression in the hippocampus is substantially reduced relative to controls, in particular in patients with the *APOE ϵ4* allele.[94] This latter observation could explain the potential interaction between diabetes and the *APOE ϵ4* genotype in the risk of dementia.

In summary, these studies of pathophysiological mechanisms suggest how diabetes-related factors and comorbid conditions can affect the brain. Vascular disease, and alterations in glucose, insulin, and amyloid metabolism seem to be important factors (figure 1), and could be potentially modifiable. For example, treatment of vascular risk factors, such as hypertension, might decrease the incidence of dementia in the context of ischaemic cerebrovascular disease.[48,95] What these studies do not show, however, is which of these pathophysiological mechanisms mainly drive the association between diabetes and dementia in a clinical setting.

Conclusion

There is convincing evidence that shows an increased risk of dementia in people with diabetes, but there are few detailed epidemiological data for risk factors. There are mechanistic studies that provide pathophysiological leads, but do not indicate which of these leads are clinically relevant. This gap in evidence between epidemiological and mechanistic studies needs to be closed. The risk factors and mechanisms that drive the association between diabetes and accelerated cognitive decline and dementia need to be identified before adequate treatment measures can be developed. This process will require longitudinal studies that include

detailed assessment of cognition, preferably in combination with neuroimaging, as well as detailed assessment of diabetes-related factors and comorbid conditions. Studies on large population-based cohorts of elderly people with diabetes and longitudinal studies of at-risk populations that examine the progress of vascular disease, metabolic syndrome, diabetes, and cognition, will be best suited for this approach.

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Authors' contributions

GJB determined the structure of the review, searched and selected the reference and prepared the first draft of the review. SS contributed to the systematic search and selection of the references and the writing. EB and CB contributed to the methodology and quality rating of the systematic review, and to the writing. PS helped to determine the concept and structure of the review, and contributed to the writing.

Conflicts of interest

We have no conflicts of interest.

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