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REVIEW

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Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies

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Abstract *Aims/hypothesis:* We systematically reviewed and summarised prospective data relating diabetes status to changes in cognitive function over time. *Methods:* Published reports of longitudinal studies that described assessment of cognitive function in people with diabetes were sought. Studies were included if they assessed cognitive function in participants with diabetes at the beginning and at follow-up. Studies were excluded if they had (1) a follow-up period of less than 1 year, (2) a rate of loss to follow-up in excess of 30%, or (3) described selected subgroups. Change in cognitive function was recorded as either the mean change in score and/or the proportion of individuals developing various degrees of change in cognitive function. A pooled estimate was calculated for the latter. *Results:* Of 1,165 abstracts and titles initially identified, 25 articles met the inclusion and exclusion criteria. Individuals with diabetes had a 1.2- to 1.5-fold greater change over time in measures of cognitive function than those without diabetes. When assessed by the Mini-Mental State Exam and the Digit Symbol Span tests, a diagnosis of diabetes increased the odds of cognitive decline 1.2-fold (95% CI 1.05–1.4) and 1.7-fold (95% CI 1.3–2.3), respectively. The odds of future dementia increased 1.6-fold (95% CI 1.4–1.8). *Conclusions/interpretation:* Compared to people without diabetes, people with diabetes have a greater rate of decline in cognitive function and a greater risk of cognitive decline. Cognitive dysfunction should therefore be added to the list of chronic complications of diabetes.

Keywords Cognition · Cognitive decline · Dementia · Diabetes · Meta-analysis · Prospective studies · Systematic review

Abbreviations DSS: Digit Symbol Substitution · MMSE: Mini-Mental State Examination · 3MS: Modified Mini-Mental

Introduction

Diabetes is a growing problem throughout the world. The global prevalence of established diabetes was estimated to be 2.8% in 2000 and is projected to be 4.4% by 2030. This prevalence rises with age; for example in the year 2000 12% of people aged 65 to 70 and 15% of people over age 80 were known to have diabetes [1]. Cognitive dysfunction represents another serious problem and is rising in prevalence worldwide, especially among the elderly. For example, in a recent Canadian study the prevalence of dementia (the most severe form of clinically diagnosed cognitive dysfunction) was estimated to be 8% for persons above 65 years of age and 34% for those aged 85 or older [2].

It is well established that diabetes is an independent risk factor for eye, kidney and neurological diseases as well as for cardiovascular morbidity and mortality. Recent evidence from several epidemiological studies suggests that it is also a risk factor for cognitive dysfunction [3–6]. However, many of these studies were cross-sectional and were thus unable to provide estimates of diabetes as a risk factor for future cognitive dysfunction. Moreover, differences in the analytical approaches and the wide variety of outcome measure used in longitudinal studies have led to varying estimates of the magnitude and importance of the relationship between diabetes and cognitive dysfunction. Indeed,

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only one [7] of the review articles that summarised the available data pertaining to this relationship [4, 6–11] provided a quantitative estimate. Such an estimate is of value to both clinicians and researchers. This systematic overview was therefore undertaken to summarise the available prospective studies and to develop an estimate of the magnitude of the risk of incident cognitive dysfunction in people with diabetes.

Materials and methods

Identification of material and inclusion/exclusion criteria

Published reports of longitudinal studies describing assessments of cognitive function in people with diabetes were sought by systematically searching various biomedical databases, talking to experts, and examining the bibliographies of relevant articles. Comprehensive electronic searches for articles were conducted by an experienced librarian and one of the authors (T. Cukierman), using Medline, EMBASE and PsycINFO, to identify studies that prospectively followed a cohort of individuals and that reported on: (1) cognitive function at baseline and at follow-up; and (2) glucose status. The diabetes-related terms and medical subject headings 'diabetes mellitus', 'glucose intolerance', 'glucose blood levels', 'glucose tolerance test', and 'blood glucose' were combined with terms related to cognitive dysfunction, e.g. 'cognition', 'mixed depression and dementia', 'presenile dementia', 'frontotemporal dementia', 'dementia' or 'multiinfarct dementia', 'senile dementia', 'cognitive defect', 'Alzheimer's disease', 'cognition disorders', 'dementia vascular', 'dementia multi infarct', or 'delerium, dementia, amnestic, cognitive disorders', as well as with 'longitudinal'or 'longitudinal studies', 'prospective' or 'meta analysis', and 'randomised controlled trials'.

Studies were included if they: (1) included a cognitive function assessment tool that was either a structured test or a clinical evaluation; (2) described the diabetes or glucose tolerance status of the participants; (3) assessed cognitive function at the beginning and subsequently; (4) provided information relating the diabetes status of the participants to their cognitive function; and (5) were written in English. Studies were excluded if: (1) loss to follow-up exceeded 30% (in studies that reported reasons for loss to follow-up, death was excluded from the estimate); (2) they followed only a subset of individuals with diabetes (e.g. those with neurological conditions or carriers of certain genetic abnormalities); or (3) they reported a follow-up period of less then one year. If studies were reported in more than one publication the most recent article that met the inclusion criteria was analysed; data from the related publications were used when necessary in order to complete the database.

The inclusion and exclusion criteria were applied to all retrieved titles or abstracts of publications, in order to arrive at a final list of eligible papers. Data from the retrieved studies were then abstracted and analysed.

Validity assessment

The selected studies were analysed according to previously published methodological criteria [12] to determine if they reported: (1) a predetermined method for selection of the participants; (2) the definition of diabetes mellitus; (3) the definition of the outcome; (4) use of the same cognitive assessment instrument in the two groups; (5) that data were collected unaware of the diabetes status (blinding); and (6) the degree of loss to follow-up.

Data abstraction

The following data were extracted from each study: age; diabetes definition; number of participants with diabetes available for analysis; number of participants without diabetes available for analysis; length of follow-up; the number and types of cognitive assessment tools used; and finally the definition used by the study for the cognitive outcome, i.e. cognitive decline or dementia.

Changes in cognitive test results were recorded as either: the mean change in score (whenever baseline and follow-up scores were available); and/or proportions of individuals developing various categories of cognitive dysfunction or clinical diagnoses such as dementia, vascular dementia or Alzheimer's dementia. The definition of dementia used in each study was accepted for this review.

Common measures of cognitive function

Cognitive function was measured using a variety of simple cognitive tests [9, 13, 14]. The most commonly used of these were: the Mini-Mental State Examination (MMSE)/ Modified Mini-Mental State (3MS) and the Digit Symbol Substitution test (DSS).

The MMSE was devised in 1975 as a tool for assessing cognitive mental status; it is widely used in the clinical setting and in epidemiological research. It has a maximum score of 30 and addresses seven different cognitive domains or functions: orientation to time (5 points), orientation to place (5 points), registration of three words (3 points), attention and calculation (5 points), recall of three words (3 points), language (8 points), visual construction (1 point) [15]. The 3MS is a modified version of the MMSE that maintains the MMSE's basic format while modifying its contents [16]. It contains a few new items, an expanded range of scores (0–100) and a modified scoring procedure. The validity of the MMSE as a screening tool for detecting dementia has been extensively studied [17]; its ability to detect changes in cognitive function for non-demented individuals has been documented mainly in the elderly [18].

The DSS measures psychomotor speed with a score ranging from 1 to 133 and requires timed translation of the numbers 1 to 9 into symbols using a key [19].

Statistical analysis

For studies reporting continuous data, the mean change in score per year for each cognitive test was calculated by dividing the mean difference in score by the follow-up period (in years). This was done separately for the diabetic and non-diabetic groups. To account for differences in baseline cognitive scores across studies, the mean annual per cent change from baseline was calculated for each score (whenever data were available). The calculated change in score for participants with diabetes was divided by the change in people without diabetes to yield a measure of the effect of diabetes on change in cognitive score. The risks for cognitive decline as measured by the MMSE and the DSS, and for clinically detected dementia in people with diabetes versus those without diabetes were separately pooled and expressed as an overall risk with 95% confidence intervals. The pooled estimates of risk were obtained by combining the separate estimates of inverse variance-weighted log risk ratio estimates from each study. Heterogeneity was assessed using the Q statistic [20]. Review Manager 4.2 for Windows (The Cochrane Collaboration, Oxford, UK) was used for analyses and graphics.

Results

Search

A total of 1,165 abstracts and titles were obtained through the database and bibliography search and reviewed by one of the authors (T. Cukierman). Of these citations, 50 met the inclusion criteria and were fully reviewed and analysed. Of these 50, 25 were excluded from the analysis because they: (1) dealt only with a subset of patients with stroke [21–23]; (2) dealt only with a subset of patients carrying the ApoE4 gene [24]; (3) had a short follow-up period [25, 26]; (4) had a high per cent of loss to follow-up [27]; or (5) described the same study and did not include additional relevant data [28–45]. The 25 remaining articles [46–70] comprised data from more than 8,656 people with diabetes, with follow-up periods ranging from 2 to 18 years.

Validity assessment

Studies were similar with respect to four of the quality measures used. Loss to follow-up ranged from 8 to 27%. Only three studies explicitly reported that data were collected without the examiner being aware of the diabetes status of the participant [46, 51, 62].

Measures of cognitive function

Cognitive function was assessed using three primary methods: (1) specific cognitive tests (Table 1); (2) a composite endpoint that was either the mean/composite score on two or more tests, or a combination of both clinical assessment and test scores; or (3) clinical assessment alone (for example incident non-specific dementia, vascular dementia or Alzheimer's dementia). Results were reported as either continuous or categorical outcomes.

Studies reporting continuous measures of cognitive decline

Table 2 lists the six studies that reported time-related changes as a continuous variable using either the MMSE or 3MS score in individuals with and without a history of diabetes [49, 51, 52, 54, 65, 69]. Individuals with diabetes experienced a consistently greater decline or lesser improvement than those without diabetes. The ratio of the relative change in score from baseline in people with diabetes compared to those without diabetes ranged from 1.2 to 1.6.

Four studies used the DSS as a continuous variable (Table 2) to assess cognitive function and three reported an adverse effect of diabetes on cognitive function over time. Three studies reported a decline ranging from 1.3 to 1.4% per year in people with diabetes. Overall, this decline was

Table 1 Cognitive function assessment tools used in studies evaluating the effect of diabetes status

Test	Reference number
Mini-Mental State Examination (MMSE) or Modified Mini-Mental State Examination (3MS)	[47, 48, 51, 52, 54, 62, 65, 69]
Digit Symbol Substitution (DSS)	[51, 52, 54, 60]
Trail Making Test (TMTA/B)	[51, 54, 62, 69, 70]
Benton Visual Retention Test (BVRT)	[51, 63]
Word recall—immediate and delayed (including auditory verbal learning test, Boston memory test, immediate and delayed word recall)	[46, 48, 51, 60, 62, 66, 70]
Verbal fluency (including: first letter, word fluency test)	[46, 60, 66, 69, 70]
Vocabulary test	[63, 66]
Word list recognition	[62, 66]
Digit span (backwards or forwards)	[46, 66]
Telephone Interview for Cognitive status (TICS)	[46]
Test of Facial Recognition (TRF)	[51]
Finger Tapping Test (FTT)	[51]
Raven's Progressive Matrices (RPM)	[51]
Paced Auditory Serial Addition Test (PASAT)	[51]
Immediate and delayed recall of a story (including story A, East Boston story)	[66]
Other tests: Boston naming, reading test, digit ordering, alpha span, symbol digit modalities test, number comparison, judgment of line orientation, standard progressive matrices	[66]

Table 2 Effect of diabetes status on changes in measurements of cognitive function over time

Test used	Ref	Age	DM definition	F/U (years)	DM			No DM			DM/ Non-DM
					n	Annual change from baseline		*n*	Annual change from baseline		
						Absolute	Relative		Absolute	Relative	
MMSE/ 3MS	[51]	69–81	History/glucose	4	55	−0.32[a]	−1.12%	768[b]	−0.27[a]	−0.90%	1.2
	[52]	>65	History/glucose	7	N/A[c]	−0.21[d,e]	N/A	3622[c]	−0.03[d,e]	N/A	N/A
	[54]	65–99(F)	History	6	402	−0.10[f]	−0.40%	5844	−0.07[f]	−0.30%	1.5
	[65]	>80	Glucose	6	38	−0.44[g,h]	−1.56%	220	−0.29[g,h]	−1.04%[i]	1.5
	[48–50]	>60	History (<5 years) glucose	2	381	−0.20[d,j]	−0.70%[i]	N/A	N/A	N/A	N/A
			History (>5 years) glucose	2	337	−0.20[d,k]	−0.80%[i]	N/A	N/A	N/A	N/A
	[69]	70.7	History/glucose	4	118	0.11[l,m]	0.40%	632[n]	0.07[l,m]	0.20%	1.6[o]
DSS	[51]	69–81	History/glucose	4	55	0.52[a]	1.20%	768[b]	1[a]	2.20%	0.5[o]
	[52]	>65	History/glucose	7	N/A[c]	−1.61[e]	N/A	3622[c]	−0.23[e]	N/A	N/A
	[60]	47–70	History/glucose	6	1349	−0.56[l,p]	−1.3%	9533	−0.41[m]	−0.90%[n]	1.4
	[54]	65–99(F)	History	6	339	−0.60[f]	−1.40%	5098	−0.40[f]	−0.90%	1.5

MMSE, Mini-Mental State Examination; 3MS, Modified Mini-Mental State Examination; DSS, Digit Symbol Substitution Test; F, female; *n*, number of participants; DM, diabetes mellitus; F/U, follow-up; OR, odds ratio; N/A—not available
[a]Adjusted for age, sex, education; [b]the comparison group had fasting glucose levels ≤ 6.1 mmol/l; [c]total number of patients analysed, diabetic/non-diabetic distribution not available; [d]the 3MS score was divided by 3.33 to obtain a score comparable to the MMSE; [e]adjusted for age, sex, education, stroke, race; [f]adjusted for age, education, baseline score, depression, vision, stroke, hypertension, heart disease, oestrogen use, self-rated health; [g]adjusted for age, sex, education, cardio-cerebrovascular disease, congestive heart failure, smoking; [h]calculated from data in article by weighted average for hypertension group and non-cases group; [i]baseline score calculated from data in article by weighted average of treated and non-treated group; [j]adjusted for age, stroke, complications; [k]adjusted for age, education; [l]score calculated from data in article by weighted average for men and women; [m]adjusted for age; [n]the comparison group had fasting glucose level <7.0 and 2-h post-challenge glucose of <7.8 mmol/l; [o]score improved over time in both groups, but by a lesser amount in those with DM; [p] adjusted for age, sex, education, use of central nervous system medication, race

Table 3 Effect of diabetes status on the risk of cognitive decline (assessed by a single instrument)

Test used	Ref	Age	DM definition	Follow-up (years)	Number		Cognitive decline	
					DM	No DM	Definition (amount of fall)	OR (95% CI)
MMSE/3MS	[48–50]	>60	History/glucose	2	585	1204	≥9%[a]	1.7 (1.2–2.3)[d]
	[54]	65–99 (F)	History	6	402	5844	≥11.5%[a]	1.0 (0.8–1.4)[e]
	[47]	>65	History	5	347	1412	≥10%[a]	1.1 (0.9–1.4)
							Score≤17	1.4 (1.0–2.0)
	[51]	69–81	History/glucose	4	55	768[b]	<15th percentile[c]	1.0 (0.5–2.2)[f]
	[62]	55–75	History	2.8	62	154	<20th percentile[c]	1.2 (0.9–1.6)[g,h]
	[69]	70.7	History/glucose	4	118	632	>6.6%[a]	M 1.3 (0.6–3.1) F 0.7(0.3–1.7)[i]
DSS	[54]	65–99 (F)	History	6	339	5098	≥7.3%[a]	1.6 (1.2–2.2)[e]
	[51]	69–81	History/glucose	4	55	768[b]	<15th percentile[c]	2.3(1.2–4.3)[f]

DM, diabetes mellitus; MMSE, Mini-Mental State Exam; 3MS, Modified Mini-Mental; DSS, Digit Symbol Substitution Test; F, female; M, male; OR, odds ratio
[a] The score fell by at least the indicated per cent of the maximum possible score (i.e. if the maximum score is 100, and the indicated per cent was 9%, the score fell by at least 9 points); [b]the comparison group had normal fasting glucose levels; [c]the fall in score exceeded the fall observed in 85% and 80% of the entire sample respectively; [d]adjusted for age, sex, education, baseline score, hypertension, acculturation, Centre for Epidemiological Studies Depression Scale score; [e]adjusted for age, education, baseline score, stroke, depression, visual impairment; [f]adjusted for age, sex, education, baseline score; [g]adjusted for age; [h]obtained by dividing the odds for cognitive decline per 5-year increase in age in people with diabetes by the odds for people without diabetes; [i] adjusted for age, education, Beck depression inventory score, presence of apolipoprotein E4 allele, baseline cognitive score, oestrogen use for women

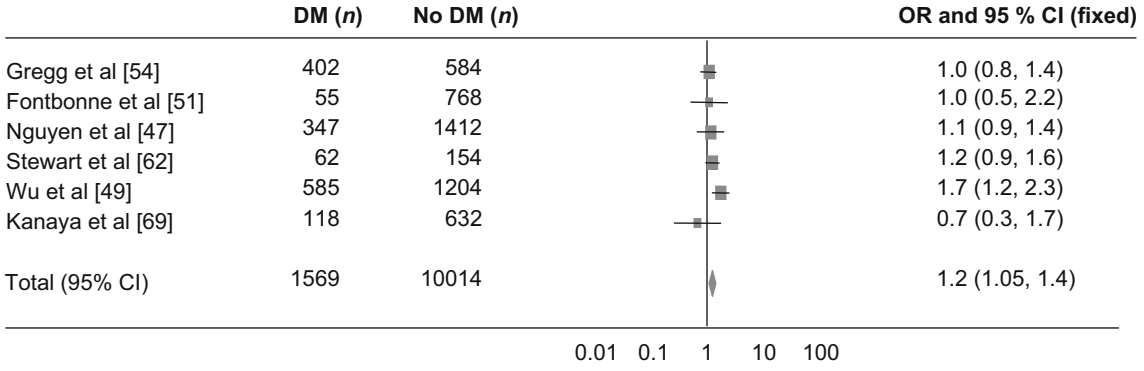

Fig. 1 Cognitive decline as assessed by the MMSE. Figure shows the risk and 95% confidence intervals of cognitive decline in diabetic (DM) versus non-diabetic (No DM) patients (as measured by the Mini-Mental State Exam), as well as the pooled estimate. Test for heterogeneity: chi square=6.73, *df*=5 (*p*=0.24), I^2=25.7%

up to 1.5 times greater than that in people without diabetes [52, 54, 60]. However, one study reported an improvement in score of 1.2% in people with diabetes; nevertheless this improvement was approximately half of the improvement experienced by the non-diabetic participants [51].

Three studies reported the effect of diabetes status on changes in a composite score that assessed cognitive function [46, 66, 70]. In these studies, individuals with diabetes had a greater absolute annual decline in score than those without diabetes; however, the differences only achieved statistical significance in one study [70].

Eight studies reported a variety of other cognitive tests, most of them reporting greater or equal cognitive change for the diabetic participants (Table 1) [46, 49, 51, 58, 63, 66, 69, 70]. Some, but not all of the tests detected a significant difference between the groups with and without diabetes.

Studies reporting categorical measures of cognitive decline

Seventeen studies divided the participants into two groups based on whether or not participants did or did not experience cognitive decline during follow-up. Cognitive decline was defined in a variety of ways that included: (1) a reduction by a particular amount relative to the baseline score; (2) a reduction below a particular threshold score; or (3) progression to clinically diagnosed dementia.

Table 3, and Figs. 1 and 2 list and display results from the six studies that used the MMSE or 3MS [47–51, 54, 62, 69] and the two studies that used the DSS [51, 54] to classify participants into those who did and did not experience cognitive decline. Figs. 1 and 2 also show the pooled estimates of risk. Compared to people without diabetes, people with diabetes were 1.2 times more likely to experience cognitive decline as measured by the MMSE/3MS (95% CI 1.0–1.4) and 1.7 times more likely to experience cognitive decline as measured by the DSS (95% CI 1.3–2.3).

Six of these studies used a composite of various other measures of cognitive status to detect cognitive decline (Table 4). This composite was used either alone or in combination with the MMSE, 3MS or DSS [46, 55, 62, 64, 68, 70]. Five of these studies reported that participants with diabetes had a higher risk of developing cognitive decline than those without diabetes; in three of these the lower limit of the 95% confidence interval exceeded 1 (i.e. it was statistically significant).

Finally, six of these 17 studies also reported the odds of decline as measured by a variety of cognitive tests [46, 49, 51, 54, 62, 69]. In these studies, diabetes status predicted an odds ratio for cognitive decline that ranged from 0.7 to 4.4. In some the lower limits of the 95% confidence

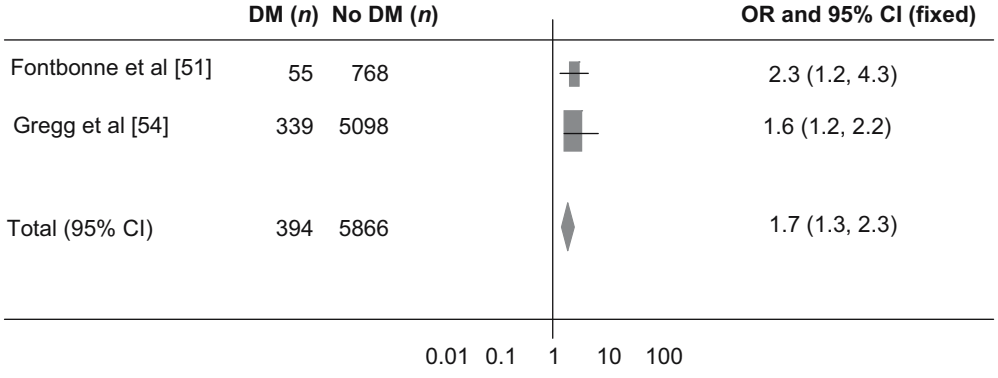

Fig. 2 Cognitive decline as assessed by the DSS. Figure shows the risk and 95% confidence intervals of cognitive decline in diabetic (DM) versus non-diabetic (No DM) patients (as measured by the Digit Symbol Substitution Test), as well as the pooled estimate. Test for heterogeneity: chi square=0.87, *df*=1 (*p*=0.35), I^2=0%

Table 4 Effect of diabetes status on the risk of cognitive decline (assessed by a composite score)

Cognitive measure	Ref	Age	DM definition	F/U (years)	Numbers		Categorical outcome	
					DM	No DM	Cut-off definition	Risk (95% CI)
Mean (5 tests)	[46]	>70 (F)	History	2	14,470[a]		<10th percentile[b]	OR 1.2 (0.97–1.5)[c]
Composite (5 tests)	[62]	55–75	History/glucose	2.8	62	154	<20th percentile[d]	OR 0.8 (0.4–1.8)
Clinical dementia rating (CDR)	[55]	74–85	History	5	101	549	Increase in rating	RR 2.2 (1.0–4.4)[e]
Clinical assessment and 3MS test	[64]	≥65	History/glucose	4–6	503	5071	Vascular cognitive impairment[f]	RR 1.8 (1.2–2.5)[g]
Cognitive impairment	[70]	66.2	History/glucose	4	~198	~4627[h]	Dementia/MCI/ probable dementia	OR 1.8 (1.1–2.8)[i]
Composite (3 tests)	[68]	60–76	History	3	37	550	MCI[j] without dementia	OR 1.5 (0.6–4.2)[k]

DM, diabetes mellitus; RR, relative risk; OR, odds ratio; F, female; 3MS, modified Mini-Mental State Examination; MCI, minimal cognitive impairment

[a]Only the total number of patients analysed was available;[b]the fall in score exceeded the fall observed in 90% of the entire sample; [c]adjusted for age, education; [d]the fall in score exceeded the fall observed in 80% of the entire sample; [e]adjusted for age, baseline score; [f]including all patients with a vascular cause for dementia and a 3MS score of less than 79; [g]adjusted for age, sex, education; [h] comparison group had a fasting plasma glucose of <6.11 mmol/l and no report of diabetes; [i]adjusted for age, treatment; [j]>1.5 standard deviations below the mean for a healthy subgroup of the sample in at least one memory test + a CDR score of 0.5; [k] adjusted for age, sex, education, hypertension, treated hypertension, cardio-cerebrovascular disease, apolipoprotein E4 allele

interval exceeded 1 (i.e. were statistically significant) [6, 46, 51, 54, 69].

Studies reporting the development of future dementia

Eight studies classified participants according to whether or not they developed dementia over time on the basis of a clinical assessment (Table 5, Fig. 3) [56–59, 64–67]. Five of these reported that people with diabetes had a higher risk of all-cause dementia than people without diabetes [56, 58, 64, 65, 67]. Overall, people with diabetes were 1.6 times more likely to develop all-cause dementia than people without diabetes (95% CI 1.4–1.8).

Six studies specifically assessed the risk of developing dementia due to Alzheimer's disease and/or vascular disease [57–59, 64, 66, 67]. All consistently reported that participants with diabetes had a higher risk of both varieties

Table 5 Effect of diabetes status on the risk of future clinically diagnosed dementia

Ref	Age	DM definition	F/U (years)	Numbers		Risk (95% CI)		
				DM	No DM	All dementia	Vascular dementia	Alzheimer's disease
[56]	>55	History/ glucose	2.1	689	4532	RR 1.9 (1.3–2.8)[a]	N/A	N/A
[57]	>65	History	7	753[b]		N/A	RR 2.8(2.6–3.0)[c]	RR 2.2 (0.97–4.9)[c]
[58]	45–99	Glucose	6.85	1455	N/A[d]	RR 1.7(1.3–2.0)[e]	N/A	M: RR 2.3 (1.5–3.3)[c] F: RR 1.4 (0.9–2.0)[c]
[59]	≥65	History	4.3	255	1007	N/A	HR 3.4(1.7–6.9)[f]	HR 1.3 (0.8–1.9)[g]
[64]	≥65	History/ glucose	4–6	503	5071	RR 1.2(0.9–1.7)[h]	RR 2.2(1.3–3.8)[h]	RR 1.2 (0.7–1.8)[h]
[66]	75	History	5.5	127	697	N/A	N/A	HR 1.6 (1.1–2.5)[i]
[67]	72–93	History/ glucose	2.9	900	1674	RR 1.5(1.0–2.2)[j]	RR 2.2(1.1–4.7)[j]	RR 1.7 (1.0–2.8)[j]
[65]	>80	Glucose	6	38	220	RR 2.1(0.99–4.4)[k]	N/A	N/A

DM, diabetes mellitus; M, male; F, female; OR, odds ratio; RR, relative risk; HR, hazard ratio; F/U,follow-up; N/A, not available

[a]Adjusted for age, sex; [b]total number of patients analysed, number of participants with diabetes not available; [c]adjusted for age; [d]data for non-diabetic population were taken from a population-based cohort; [e]adjusted for age, sex; [f]adjusted for sex, education, hypertension, heart disease, LDL level, smoking, ethnicity; [g]adjusted for sex, education, presence of apolipoprotein E4 allele, ethnicity; [h]adjusted for age, sex, education; [i]adjusted for age, sex, education and interactions of these with time; [j]adjusted for age, education, apolipoprotein E4 status, smoking, alcohol, diabetes medication; [k]calculated from incidence rates data in article

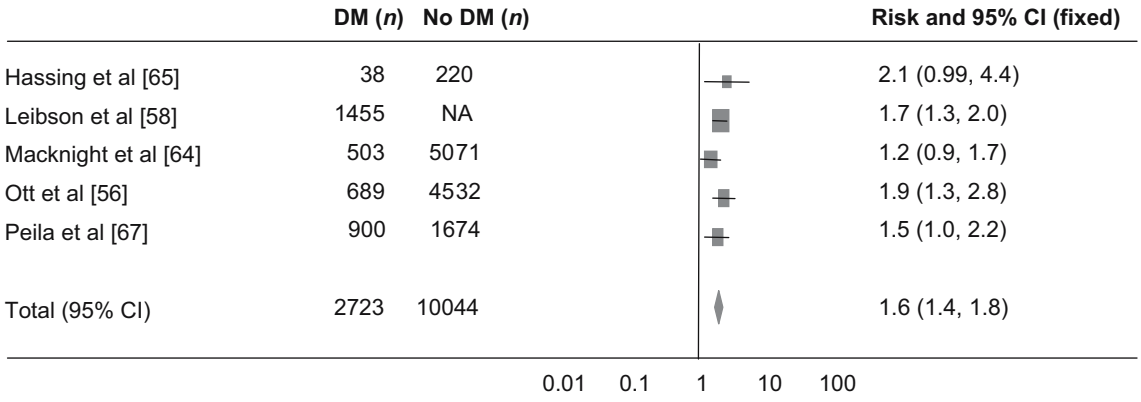

Fig. 3 Development of future dementia. Figure shows the risk of future dementia in diabetic (DM) versus non-diabetic (No DM) patients, as well as the pooled estimate. Test for heterogeneity: chi square=4.02, *df*=4 (*p*=0.40), I^2=0.6%

of dementia than non-diabetic participants, with risks ranging from 1.2 to 2.3 for Alzheimer's disease and 2.2 to 3.4 for vascular dementia.

Discussion

This systematic overview of prospective studies supports the conclusion that, compared to people without diabetes, people with diabetes have: (1) a greater rate of decline in cognitive function; (2) a 1.5-fold greater risk of cognitive decline; and (3) a 1.6-fold greater risk of future dementia. Interestingly, the included studies reported a similar degree of cognitive decline, despite differences in analytic approaches and cognitive assessment tools. Furthermore, these studies probably underestimated the impact of diabetes on cognitive function because they generally excluded cognitively impaired individuals at baseline, and may therefore have 'selected for' healthier individuals with lower risk of cognitive decline. Another factor suggesting that the reports underestimated the effect of diabetes on cognitive decline is the fact that most of the studies did not include information on people who died or who were lost to follow-up, when follow-up success itself could well be linked to good cognitive function. Indeed, in one study, which did report diabetes status of individuals lost to follow-up, diabetic participants had a higher mortality and/or lower follow-up rates than those without diabetes [55].

These findings are supported by previous reviews of the available longitudinal studies [3, 4, 6]. They are also supported by the large Framingham study [71] and the Adult Health Study [72]. In the Framingham Study, 2,123 subjects aged 55 to 88 completed a neuropsychological test battery during either the 14th or 15th biennial examination. People with diabetes status were more likely to achieve scores below the 25th percentile on most tests than were non-diabetic individuals. The Adult Health Study followed a cohort of atomic bomb survivors from Hiroshima and Nagasaki. After 34 to 39 years of follow-up, 1,774 participants were screened for dementia. Compared to non-diabetic individuals, diabetes increased the risk of vascular dementia and Alzheimer's dementia 1.3 and 4.4-fold, respectively. These two studies were excluded from this review because they did not report baseline cognitive measurements.

A number of possibilities may explain the association between diabetes and cognitive decline.

First, diabetes is well established as a risk factor for cerebrovascular disease; it is also associated with hypertension and dyslipidaemia. Thus, a relationship between cognitive change and diabetes may be mediated through cerebrovascular disease. This may be more pronounced in the older age group and requires careful consideration when assessing patients.

Second, depression occurs more frequently in people with diabetes [73] and is difficult to differentiate clinically from dementia and early cognitive decline [74–77]. However, at least one of the studies [54] reported an association between diabetes and cognitive decline even after adjustment for depression.

Third, hypoglycaemia may affect cognitive function. However, in contrast to the acute negative effect of hypoglycaemia on cognition, there is little evidence to support chronic cognitive impairment secondary to hypoglycaemia. Indeed, intensive treatment regimens that were associated with increased hypoglycaemic episodes in individuals with type 1 diabetes did not adversely affect cognition [78].

Fourth, hyperglycaemia may also contribute to chronic cognitive impairment. Post mortem studies of senile plaques from the brains of people with Alzheimer dementia found metabolic oxidation products associated with hyperglycaemia [79, 80]. Experimental studies in animal models and in humans without diabetes have shown that poor glucose regulation after a glucose challenge test was associated with poorer performance on a variety of cognitive tests, the effect being more pronounced in the older age group [81]. Moreover, two of the studies included in this review reported that participants with impaired fasting glucose or impaired glucose tolerance experience more cognitive decline than participants without, further supporting a link between cognitive decline and hyperglycaemia [51, 69, 70]. Finally, prospective epidemiological studies also show a relationship between cognitive decline and clinical markers associated

with hyperglycaemia, e.g. use of glucose-lowering medication, diabetes duration and diabetes complications [46, 48, 49, 54, 56, 64].

The overview presented in this study is limited by several factors. It is possible, for example, that studies that did not show an association between diabetes status and cognitive decline may not have been published as often as studies that did. However, many of the studies analysed by us were prospective cohort studies, which examined many risk factors for cognitive decline, and not just diabetes. This makes it unlikely that a lack of an association with diabetes would lead to non-publication. Another limiting factor is that many of the studies analysed used the MMSE/3MS as a measure of cognitive function. This instrument (which was designed as a tool for assessing global cognitive function) has a limited ability to detect changes in specific cognitive domains such as attention and processing speed [17, 82]. As these domains may be selectively impaired in people with diabetes the MMSE/3MS will underestimate the impact of diabetes on cognitive function [10]. This possibility is supported by the fact that the overall estimated effect of the MMSE/3MS was smaller than the overall estimate obtained from studies that used the DSS.

The study is also limited by the differences in the studies included with respect to: (1) the definition of a clinically meaningful decline in cognitive function; (2) identification of people with and without diabetes; (3) age groups that were studied; (4) cognitive assessment tools employed; (5) degree of statistical adjustment for confounders; (6) degree of cognitive impairment permitted in studied participants at baseline; and (7) completeness of follow-up that ranged from 73 to 92%. Despite these differences, only two studies reported that diabetes non-significantly reduced the risk for cognitive decline. In one study, this finding was only noted in young participants, while findings in older participants were consistent with the results from the other studies [62]. In the other study, this finding was only noted for women, and only in certain cognitive tests. The large confidence interval and wide variability of scores between tests reported in this study suggest that a larger sample size could possibly have altered the results [69]. The consistency of our results, despite the differences in the studies, highlights the robustness of the conclusion that diabetes is indeed a risk factor for cognitive decline.

Despite this relationship, there is no evidence to date that diabetes management affects the rate or nature of cognitive dysfunction. Indeed, a recent review of the effect of therapy concluded that no studies were appropriate for inclusion in meta analysis [4]. Nevertheless, the results of the prospective studies summarised here suggest that cognitive dysfunction should be considered as yet another chronic consequence and disabling manifestation of diabetes. They highlight the importance of including measurements of cognitive function in future studies of glucose-lowering and other therapies in people with diabetes, to determine whether or not this decline can be mitigated.

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