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The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations

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Abstract

Type 2 diabetes and dementia in the elderly are major public health problems. Cross-sectional studies have suggested that these two conditions may be inter-related, but the nature of this association is uncertain. Causation can only be established through studies with a longitudinal design, taking into account the many potential confounding factors in any study of cognition. A literature search has identified 10 studies (nine population-based and one of case-controlled design) that included a definable diabetic population and assessments of cognitive function at baseline and at follow-up. These 10 studies utilised a combination of domain-specific cognitive assessments and a clinical diagnosis of dementia in the assessment of cognitive function. Diabetes was associated with either an accelerated cognitive decline or an increased incidence of dementia in eight of nine of the population-based studies. One study demonstrated a relationship between diabetes and vascular cognitive impairment, but not with other types of dementia. No association between type 2 diabetes and cognitive decline was demonstrated in the case-controlled study. These studies provide compelling evidence to support the view that people with type 2 diabetes are at increased risk of developing cognitive impairment in comparison with the general population.
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1. Introduction

Type 2 diabetes and dementia are common in the elderly and both are often progressive and disabling conditions. Ten percent of people over the age of 65 years develop dementia, rising to more than 50% of people over the age of 85 years (Evans et al., 1989; Geldmacher and Whitehouse, 1996). Greater than 10% of the elderly population in the USA have type 2 diabetes, the prevalence of which rises with increasing age, and a global pandemic of this condition is evident (Harris, 1998; Harris et al., 1998).

Cognitive function (particularly memory) declines with age, although the rate of decline is not distributed uniformly within the population. For a minority this progresses in severity to cause disability until dementia is diagnosed. A possible relationship between cognitive decline and diabetes has been posited since the discovery of insulin (Miles and Root, 1922). In type 1 diabetes, this relationship has traditionally been thought to be related to the frequency of exposure to severe hypoglycaemia (Perros and Deary, 1999), although two observational studies have related psychomotor slowing to hypertension, microvascular complications and duration of diabetes (Ferguson et al., 2003; Ryan et al., 2003). The relationship between type 2 diabetes and accelerated cognitive decline, however, is more complex and is unlikely to be associated with exposure to hypoglycaemia, which is a relatively infrequent occurrence. Cross-sectional studies have suggested an association between type 2 diabetes, cognitive decline (particularly in aspects of verbal memory) and dementia (Strachan et al., 1997a; Stewart and Liolitsa, 1999) but a causal relationship can only be established through examination of the rate of change of cognitive function within an individual, which requires a longitudinal study design. In this paper the published longitudinal data relating type 2 diabetes to cognitive function are reviewed.

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2. Identification of relevant published research

Medline, PsychINFO and The Cochrane Library databases were interrogated to identify relevant studies published since 1966 in peer reviewed journals. The bibliographies of all relevant original and review articles were examined for other suitable studies.

Twelve longitudinal studies were identified in which an assessment of cognitive function had been made in people with diabetes. Ten studies fulfilled the following criteria: inclusion of an appropriate control group, adequate provision had been made for the diagnosis of type 2 diabetes, baseline cognitive function had been recorded and an adequate attempt had been made to control for confounding factors. These studies demonstrated considerable heterogeneity in terms of inclusion criteria, study design and cognitive test batteries and therefore a formal meta-analysis of data was not attempted. Of the remaining two population-based longitudinal studies of diabetes, one included a cross-sectional assessment of cognitive function during the follow-up period, but no baseline assessment of cognition had been made (Elias et al., 1997). The remaining study demonstrated a relationship between accelerated cognitive decline and a composite endpoint diabetes and/or cardiovascular disease but data for diabetes were not presented separately (Launer et al., 1996). The 10 key studies are discussed in detail.

3. Longitudinal studies

In four of the nine population-based studies, cognition was assessed using a combination of Mini Mental State Examination (MMSE) and a cognitive test battery (Haan et al., 1999; Gregg et al., 2000; Fontbonne et al., 2001; Knopman et al., 2001). Five further population-based studies utilised a clinical diagnosis of dementia (Yoshitake et al., 1995; Ott et al., 1999; Luchsinger et al., 2001; MacKnight et al., 2002; Peila et al., 2002). One longitudinal case-controlled study used a small cognitive test battery as a measure of cognition (Robertson-Tchabo et al., 1986). The salient features and results of each study will be discussed in turn. Demographic details are shown in Table 1.

3.1. Population-based studies utilising a cognitive test battery

In the Epidemiology of Vascular Aging Study (Fontbonne et al., 2001), participants in Nantes, France were divided into three groups according to baseline glycaemic status: normal fasting blood glucose, impaired fasting glucose (6.1–6.9 mmol/l) or diabetes. A broad battery of eight domain specific tests was employed, under blinded conditions over 4 years of follow up. These were the Trail Making Test part B (TMTB) (visual attention), Auditory Verbal Learning Test (AVLT) (immediate verbal memory), Test of Facial Recognition (TFR) (visual attention), Digit Symbol Substitution (DSS) (sustained attention, psychomotor speed and logical reasoning), Finger Tapping Test (FTT) (psychomotor speed), Benton Visual Retention Test (BVRT) (immediate non-verbal memory), Raven's Progressive Matrices (RPM) (logical reasoning) and the Paced Auditory Serial Addition Test (PASAT) (auditory attention). After adjustment for age, sex and education, the people with diabetes exhibited a greater than twofold higher rate of "serious worsening of cognitive function" (OR>2, $P<0.05$), defined as the worst 15% of the distribution of score differences, in four of the eight tests (TMTB, AVLT, TFR, FTT), when compared with people with baseline normal glucose, or impaired fasting glucose. This well designed study provides the most detailed cognitive assessment of any longitudinal study of type 2 diabetes that has been published to date.

Table 1
Demographic details and criteria for diagnosis of diabetes for longitudinal studies of cognitive decline in type 2 diabetes

Reference	Country of study	Subjects		Study design	Length of follow-up (years)	Mean age of entire group (years)	Method of diabetes diagnosis
		Total	Diabetes				
Fontbonne et al. (2001)	France	926	55	Population based	4	65 (59–71)	Self-report FBG
Knopman et al. (2001)	USA	10,963	1329	Population based	6	57 (47–70)	Self-report FBG > 126 mg/dl medication review
Gregg et al. (2000)	USA	9679	682	Population based	6	71.7 (± 5.0)	Self-report Medication review
Haan et al. (1999)	USA	5888	Ns	Population based	7	ns	Self-report Physician diagnosis 2 h OGTT
Luchsinger et al. (2001)	USA	828	70	Population based	4	74 (± 6)	Self-report Medication review
Ott et al. (1999)	Netherlands	6370	692	Population based	2	68.9 (8.8)	2 h OGTT Medication review
Peila et al. (2002)	Hawaii	2574	900	Population based	3	77 ± 4.0	Self-report Medication review 2 h OGTT
MacKnight et al. (2002)	Canada	5574	503	Population based	5	74 ± 6.4	Self report Medication review RBG>200 mg/dl
Yoshitake et al. (1995)	Japan	1262	255	Population based	7	75.6 (± 5.9)	Ns
Robertson-Tchabo et al. (1986)	USA	662	52	Case-control	12	62.2 (33.0–86.7)	National Diabetes Data Group 1979

Mean age given as ± S.D. or range; FBG = Fasting blood glucose; RBG = Random blood glucose; OGTT = Oral glucose tolerance test; ns = not stated.

Cognitive decline was assessed in 9769 community dwelling white North American women aged 65–99 years in the Study of Osteoporotic Fractures (Gregg et al., 2000). The MMSE (modified to exclude basic orientation questions, hence giving a maximum score of 26 rather than the usual score of 30), DSS and TMTB were used to assess cognition. After controlling for confounding factors, women with type 2 diabetes had an approximately twofold higher risk of major cognitive decline in all three tests, as defined as the greatest 10th percentile reduction in performance from initial follow-up. However, a major limitation to this study was that the diagnosis of diabetes relied on self-report or review of medication, and no objective measurements of blood glucose were made.

In the Atherosclerosis Risk in Communities Study (ARIC) (Knopman et al., 2001), cognitive function was assessed in an unselected biracial North American population of 10,963 middle aged people at baseline and at follow-up after 6 years. Cognitive tests administered were the Delayed Word Recall (DWR) (verbal learning and recent memory) and DSS from the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The First-letter Word Fluency Test (WFT) (sustained attention, psychomotor speed and logical reasoning) was also administered. Multivariate analysis controlling for confounding factors (demographic details, hypertension, hyperlipidaemia, medication, cardiovascular disease and stroke, carotid intimal thickness and smoking history) revealed a small but significant decline over the follow up period in performance of DSS (mean test score decline 3.94 vs. 2.90) and DWR (mean test score decline 1.35 vs. 0.67) (both $P<0.05$), but not in WFT in those with diabetes in all age groups, compared with non-diabetic controls. Hypertension (defined as blood pressure greater than 140/90mm Hg or the use of antihypertensive treatment) was associated with a small but significantly poorer performance of the DSS alone ($P<0.05$) compared with the non-hypertensive group in older participants.

The Cardiovascular Health Study (Haan et al., 1999) was a population-based cohort study of 5888 North American people aged over 65 years with a duration of follow up of 7 years. A limited cognitive test battery was administered, consisting of a modified MMSE (scored 0 to 100) (Teng and Chui, 1987) and the DSS. Diabetes was associated with poorer performance in the DSS with a decline (change in test score -2.1 vs. -0.3, $P<0.0001$) over 7 years compared to people who did not have diabetes. This effect was further enhanced in the presence of the Apolipoprotein E $\varepsilon 4$ genotype.

3.2. Population-based studies utilising a clinical diagnosis of dementia

Luchsinger et al. (2001) reported a longitudinal study with annual follow-up for 4 years in a random sample of 1799 non-demented North American elderly people. The diagnosis of dementia was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition (American Psychiatric Association, 1994). Diabetes was associated with stroke-associated dementia (hazard ratio 3.4, 95% CI: 1.70–6.91) and to a composite outcome of Alzheimer's disease and cognitive deficit without dementia (hazard ratio 1.6, 95% CI 1.2–2.1). The risks were particularly notable in those treated with insulin compared to oral antidiabetic medications. The major limitation to this study is the reliance of self-reporting of diabetes and other risk factors (encouraging under-diagnosis) and the high proportion of participants (30%) lost to follow-up.

Ott et al. (1999) followed 6370 non-demented, elderly people for 2 years. The diagnosis of Alzheimer's disease was made following the NINCDS-ADRDA criteria (McKhann et al., 1984) and the NINDS-AIREN criteria (Roman et al., 1993) for vascular dementia. Other dementias were classified according to DSM-III criteria (American Psychiatric Association, 1980). After adjustment for confounding factors, diabetes doubled the risk of development of all types of dementia (RR 1.9, 95% CI 1.3–2.8), of Alzheimer's disease (RR 1.9, 95% CI 1.2–3.1) and of vascular dementia (RR 2.0, 95% CI 0.07–5.6). A limitation to the study is that brain imaging was not obtained as part of the diagnostic work-up for dementia. As such, cerebrovascular pathology may have been an underlying feature in those given a diagnosis of Alzheimer's disease.

The Honolulu–Asia Aging study (Peila et al., 2002) followed 2574 elderly non-demented Japanese–American men for 3 years. The relationship between diabetes, APOE $\varepsilon 4$ genotype and development of dementia was examined. Dementia was diagnosed according to DSM-III criteria (American Psychiatric Association, 1980). After adjustment for confounding factors, diabetes increased the risk of development of dementia (RR 1.5, 95% CI 1.01–2.2) and this effect was further enhanced by the presence of the APOE $\varepsilon 4$ allele (RR 4.4, 95% CI 1.9–10.0), although the risk of developing vascular dementia was reduced and became non-significant.

The Canadian Study of Health and Aging (MacKnight et al., 2002) followed 5574 elderly non-demented community dwelling people for 5 years. The mini-mental state examination (3MS) was used as a screening tool for dementia at baseline and follow-up. People scoring less than 79 out of 100 and a random sample of those scoring higher than 79 were invited for clinical assessment. Dementia was diagnosed according to DSM-III criteria (American Psychiatric Association, 1980). Alzheimer's disease was diagnosed according to NINCDS-ADRDA (McKhann et al., 1984) criteria and vascular dementia was diagnosed using NINDS-AIREN (Roman et al., 1993) criteria. Diabetes was not associated with greater risk of development of all types of dementia or Alzheimer's disease. Diabetes was associated with an increase in the development of vascular cognitive impairment (RR 1.62, 95% CI 1.12–2.33). The study was limited by failure to adequately screen for diabetes, opting

for a random blood glucose measurement only. Analysis was not adjusted for smoking and drinking, two established risk factors for the development of cognitive impairment (Launer et al., 1996).

The Hisayama Study (Yoshitake et al., 1995) followed 887 people in Japan (70 with diabetes) closely for 7 years with the objective of determining risk factors for the subsequent development of dementia. In multivariate analysis, diabetes was associated with a higher incidence of Alzheimer's disease (RR 2.18, 95% CI: 0.97–4.90) as defined by DSM, third edition criteria (American Psychiatric Association, 1980), and vascular dementia (RR 2.09, 95% CI: 0.91–4.81) as defined by NINDS-AIREN criteria (Roman et al., 1993), although both findings failed to reach statistical significance. Lack of specific data regarding the group of people with diabetes hinders further interpretation of the results in this subgroup.

3.3. Case-controlled study utilising a cognitive test battery

Robertson-Tchabo et al. (1986) reported 12-year follow up data from the Baltimore Longitudinal Study of Aging in 52 American men with diabetes compared with 610 matched non-diabetic controls. Two tests of cognitive function were administered: the Benton Visual Retention Test (immediate non-verbal memory) and the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS). Cross-sectional and longitudinal comparisons found no evidence of an association between diabetes and a decline in cognitive function. However, the group studied was not representative of a definable population, introducing a significant potential selection bias. The sample size was small at baseline and 30 subjects with diabetes (58%) had been lost to follow-up by the time of the 12-year assessment.

4. Methodoligical and statistical limitations

4.1. Statistical limitations of longitudinal studies

An important limitation in all longitudinal studies is the vulnerability to survivor bias. In several studies, subjects with diabetes or those who had poor cognitive function at baseline were more likely not to attend for follow-up or to have died, leading to a potential underestimation of the effect of diabetes on cognitive function (Haan et al., 1999; Gregg et al., 2000; Knopman et al., 2001; MacKnight et al., 2002). Annual reduction of data can reduce but not eliminate this potential source of bias (Haan et al., 1999; Luchsinger et al., 2001).

Longitudinal studies are better adapted than cross-sectional studies to investigate an ageing effect and a cohort effect, although the relationship may be blurred in these studies by a learning effect, obscuring any true underlying decline in cognitive ability (Strachan et al., 1997b). The improved performance that is observed when tests are administered multiple times occurs even if test items are changed (parallel versions), and therefore is likely to be caused by an implicit learning of test-taking skills. Thus, follow-up must be infrequent over an extended period of time or compared cross-sectionally in two groups with a similar learning effect (for example, longitudinal data from two age groups within the same study). Learning effect does not decline with age but can vary with different risk groups, introducing another potential source of bias (Small et al., 1999). Some tests of cognitive function may be particularly vulnerable to this learning effect, which may explain why some areas of cognitive function appear to be more vulnerable to decline in a longitudinal study design while others are seemingly spared (Fontbonne et al., 2001).

4.2. Confounding factors and moderators of cognitive function

It is not clear whether the risk of cognitive impairment is globally associated with type 2 diabetes or whether it is linked to particular subgroups of people with other conditions affecting cognitive function, or conditions associated with diabetes or its treatment (Strachan et al., 1997a). It is impossible to state that chronic hyperglycaemia per se causes cognitive impairment without taking into account all of these potential confounding factors (Colsher and Wallace, 1991). Several small cross-sectional studies have demonstrated only limited cognitive dysfunction in people with type 2 diabetes after correcting for potential confounding factors (Cosway et al., 2001; Asimakopoulou et al., 2002). Lifestyle factors such as alcohol intake and smoking history are significant moderators of cognitive function in the general population (Launer et al., 1996). Inadequate adjustment for gender and pre-morbid IQ has been made in previous cross-sectional studies (Strachan et al., 1997a; Asimakopoulou et al., 2002), but these factors were taken into account in most of the longitudinal studies discussed in the present review and are shown in Table 2.

Medical conditions, such as hypertension, depression and vascular disease, which often co-exist with type 2 diabetes in the elderly, are important moderators of cognitive function (Croxson and Jagger, 1995; Helkala et al., 1995). An association between hypertension, both in mid-life and in old age, and poor cognition in later life has been demonstrated in several cross-sectional studies (Elias et al., 1993; Launer et al., 1995; Carmelli et al., 1998) and mounting evidence of a causal relationship is provided by data from longitudinal studies (Knopman et al., 2001). A validated assessment of depression should be included in all studies of cognition. Depression can be mistaken for dementia (and vice versa) (Swainson et al., 2001) and is associated with defects of memory and learning (Reding et al., 1985; Austin and Mitchell, 1997; Visser et al., 2000) and occurs more frequently in type 2 diabetes, particularly in those with diabetes-related complications (Anderson et al., 2001).

Table 2
Confounding factors taken into account in each longitudinal study of cognitive decline in type 2 diabetes

	Age	Gender	Education	Smoking	Alcohol	Hypertension/BP	Cardiovascular disease	Depression
Fontbonne et al. (2001)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Knopman et al. (2001)	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Gregg et al. (2000)	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes
Haan et al. (1999)	Yes	Yes	Yes	No	No	Yes	Yes	No
Yoshitake et al. (1995)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Luchsinger et al. (2001)	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Ott et al. (1999)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Peila et al. (2002)	Yes	N/A	Yes	Yes	Yes	Yes	Yes	No
MacKnight et al. (2002)	Yes	Yes	Yes	No	No	Yes	Yes	No
Robertson-Tchabo et al. (1986)	Yes	Yes	Yes	No	No	No	No	No

N/A: not applicable.

Apolipoprotein ε4 allele is an independent risk factor for cognitive decline and dementia (Noguchi et al., 1993; Kalmijn et al., 1996; Hofman et al., 1997) particularly when associated with high systolic blood pressure, ABPI, atherosclerosis of internal carotid artery, and diabetes (Kalmijn et al., 1996; Haan et al., 1999). The ε4 allele is also associated with insulin resistance in non-diabetic humans. It may therefore be a shared risk factor both for type 2 diabetes and cognitive decline (Uusitupa et al., 1996; Peila et al., 2002), and is potentially a powerful confounding factor in the reported studies.

It may not be possible to separate these moderators of cognitive function from type 2 diabetes because they often form an integral part of the disease and it is likely that these factors act synergistically to cause impairment of cognitive function. While none of the studies reported are without their methodological flaws, these potential confounding factors may therefore be more relevant in small cross-sectional studies than in large population-based longitudinal studies.

4.3. Diabetes-specific variables

Several longitudinal studies have relied on self-report of diabetes (Table 1). This is relevant in that in the elderly population up to one-third of diabetes remains undiagnosed (Franse et al., 2001) and those with undiagnosed diabetes have the same risk of morbidity and mortality as those in whom the condition is known (Harris, 1993). It should be noted that none of the longitudinal studies discussed above made an attempt to distinguish between type 1 and type 2 diabetes. However, few people were receiving insulin therapy and most participants were elderly. It is therefore unlikely that a significant proportion of people studied had type 1 diabetes.

Inappropriate test procedures such as failure to test blood glucose during psychometric testing can introduce bias in favour of the control group. Cognitive function declines during hypoglycaemia (Deary, 1993) and also during moderate hyperglycaemia in people with type 2 diabetes (Sommerfield et al., 2003; Greenwood et al., 2003). No information on the temporal relationship between blood glucose testing, if it was performed, and administration of the cognitive test battery was provided in all of the studies discussed above.

Longer duration of diabetes may also be associated with poorer cognitive performance (Elias et al., 1997; Gregg et al., 2000) although it is always difficult to ascertain the duration of type 2 diabetes with any accuracy as it may have been present for several years before diagnosis (Harris et al., 1992). None of the longitudinal studies reviewed in this article have examined the relationship between cognition and the vascular complications of diabetes.

Several studies have suggested an association between glycaemic control and cognitive performance (Gradman et al., 1993; Meneilly et al., 1993; Sotaniemi et al., 1995; Naor et al., 1997), although these studies all have significant methodological flaws. At present, no convincing link exists between treatment modality and the development of cognitive impairment or dementia (Areosa Sastre and Grimley Evans, 2003). This is the subject of an ongoing detailed Cochrane review which has highlighted the need for future randomised controlled trials of therapeutic intervention in type 2 diabetes to include an assessment of cognitive function over time (Areosa Sastre and Grimley Evans, 2003).

4.4. The choice of appropriate psychometric tests

One problem with the choice of cognitive tests is determining what constitutes a clinically or functionally important decline in cognitive function. A change in cognitive function demonstrated in a particular test lacks the detail and specificity of diagnosing a disease (e.g. Alzheimer's disease) and may not be directly relevant to clinical practice. However, it avoids the subjective judgement that is involved in disease diagnosis, so results are less open to interpretation (Morris et al., 1999). Many changes in cognitive function observed in longitudinal studies are of relatively small magnitude. However, mild cognitive impairment is an established risk factor for the subsequent development of dementia (Petersen et al., 2001) and may therefore be considered to be clinically relevant.

Several longitudinal studies have favoured the diagnosis of dementia as an endpoint rather than using more sensitive psychometric testing (Yoshitake et al., 1995; Luchsinger et al., 2001; Ott et al., 1999; Peila et al., 2002; MacKnight et al., 2002).

Psychometric tests are more sensitive to cognitive decline than the MMSE, which is designed to screen for dementia rather than to measure subtle changes in cognitive decline (Folstein et al., 1975; Tombaugh and McIntyre, 1992). All studies of acquired cognitive impairment must take into account previous intelligence and education in order to avoid ceiling or floor effects at baseline. A relatively insensitive test such as the MMSE is likely to produce a ceiling effect and have reduced sensitivity to detect a subtle decline in cognitive function in people with high educational achievement.

5. Conclusions

Compelling evidence now exists from both cross-sectional and longitudinal studies to support the view that people with diabetes are at increased risk of developing cognitive impairment in comparison with the general population.

This may be related to the duration of diabetes but to date very little evidence exists to suggest a relationship between cognitive decline and treatment modality. This issue is of major clinical relevance to people with diabetes and to public health in general. Even modest reductions in risk factors for the development of either condition could have a major public health impact for future generations.

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