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Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia (Review)

Areosa Sastre A, Vernooij RWM, González-Colaço Harmand M, Martínez G

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Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia
(Review)

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[Intervention Review]

Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia

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ABSTRACT

Background

Prevention of cognitive impairment and dementia is an important public health goal. Epidemiological evidence shows a relationship between cognitive impairment and Type 2 diabetes mellitus. The risk of dementia increases with duration of disease. This updated systematic review investigated the effect on cognitive function of the type of treatment and level of metabolic control in people with Type 2 diabetes.

Objectives

To assess the effects of different strategies for managing Type 2 diabetes mellitus on cognitive function and the incidence of dementia.

Search methods

We searched ALOIS (the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG)), the Cochrane Library, MEDLINE, Embase, PsycINFO, CINAHL and LILACS on 15 October 2016. ALOIS contains records from all major health care databases, (CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, LILACS), as well as from many trials' registers and grey literature sources.

Selection criteria

We included randomised controlled trials (RCTs) which compared two or more different treatments for Type 2 diabetes mellitus and in which cognitive function was measured at baseline and after treatment.

Data collection and analysis

Two review authors independently extracted data and assessed the quality of the included RCTs. We pooled data for comparable trials and estimated the effects of treatment by using risk ratios (RRs) and mean differences (MDs), according to the nature of the outcome. We assessed the quality of the evidence using GRADE methods.

Main results

We identified seven eligible studies but only four provided data we could include in efficacy analyses. Two of these studies compared intensive versus standard glycaemic control and two compared different pharmacological treatments. All studies were at unclear risk of bias in at least two domains and one large study was at high risk of performance and detection bias.

(a) Two studies with 13,934 participants at high cardiovascular risk provided efficacy data on intensive versus standard glycaemic control. A third study with 1791 participants provided additional data on hypoglycaemic episodes and mortality. There is probably no difference between treatment groups in the number of participants who decline by at least 3 points on the Mini-Mental State Examination (MMSE) over five years (RR 0.98, 95% CI 0.88 to 1.08; 1 study; n = 11,140; moderate-quality evidence); and there may also be little or no difference in the incidence of dementia (RR 1.27, 95% CI 0.87 to 1.85; 1 study; n = 11,140; low-quality evidence). From another study, there was probably little or no difference in MMSE score after 40 months (MD -0.01, 95% CI -0.18 to 0.16; 1 study; n = 2794; moderate quality evidence). Participants exposed to the intensive glycaemic control strategy probably experience more episodes of severe hypoglycaemia than those who have standard treatment (RR 2.18, 95% CI 1.52 to 3.14; 2 studies; n = 12,827; moderate-quality evidence). The evidence from these trials suggests that the intensity of glycaemic control may have little or no effect on all-cause mortality (RR 0.99, 95% CI 0.87 to 1.13; 3 studies; n = 15,888; low-quality evidence).

(b) One study with 156 participants compared glibenclamide (glyburide) with repaglinide. There may be a small advantage of glibenclamide on global cognitive function measured with the MMSE after 12 months (MD -0.90, 95% CI -1.68 to -0.12; low-quality evidence). No data were reported on the incidence of dementia, hypoglycaemic events or all-cause mortality.

(c) One study with 145 participants compared rosiglitazone plus metformin to glibenclamide (glyburide) plus metformin over 24 weeks. It reported only on cognitive subdomains and not on global cognitive function, incidence of MCI or dementia, hypoglycaemic events or all causes of mortality.

Authors' conclusions

We found no good evidence that any specific treatment or treatment strategy for Type 2 diabetes can prevent or delay cognitive impairment. The best available evidence related to the comparison of intensive with standard glycaemic control strategies. Here there was moderate-quality evidence that the strategies do not differ in their effect on global cognitive functioning over 40 to 60 months.

PLAIN LANGUAGE SUMMARY

Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia

Background

Dementia is a global healthcare concern. Type 2 diabetes mellitus — a form of diabetes which becomes commoner with older age — increases the risk of developing dementia. Type 1 diabetes, which typically begins earlier in life, is always treated with insulin; but there are a variety of different ways of treating Type 2 diabetes, including lifestyle changes and different medications. We wanted to find out if some ways of treating Type 2 diabetes were better than others in terms of preventing either dementia or less serious decline in cognition (memory and other thinking skills).

What we did

We searched medical databases for clinical trials in which participants had been assigned at random to different treatments for Type 2 diabetes and in which cognition had been measured at the beginning and end of the trial. We were only interested in treatments for Type 2 diabetes which are recommended by international clinical practice guidelines (CPGs). We analysed data from the studies we found, looking for effects on dementia and cognition, death rates and the side effect of hypoglycaemia, which is when blood glucose levels fall too low and which can be a result of treatment.

Key results

We found seven randomised trials suitable for inclusion in this review, but we could only get data on cognition from four of them. Of these, the two larger studies had a total of 13,934 participants and compared a standard treatment strategy with a more intensive strategy which aimed to keep blood glucose lower. Two smaller studies, which each had approximately 150 participants, compared different drug treatments, but in both studies one of the treatments was a drug which is not generally considered suitable for older patients. We found no good evidence that any of the treatments in these studies was clearly superior to any other for preventing dementia or cognitive decline. An intensive treatment strategy was more likely than standard treatment to cause hypoglycaemia, but there were no differences in death rates.

Quality of evidence

We judged the quality of the evidence for all outcomes to be low or moderate due to risk of bias in the included studies, small sample sizes, and imprecise estimates of the effects. This means that our confidence in the results is limited.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Glibenclamide (glyburide) compared to Repaglinide for Type 2 diabetes

Glibenclamide (glyburide) compared to Repaglinide for Type 2 diabetes

Patient or population: patients with Type 2 diabetes

Settings: general population

Intervention: Glibenclamide (glyburide)

Comparison: Repaglinide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Repaglinide	Glibenclamide (glyburide)				
Global cognitive function measured by MMSE at 12 months		The mean MMSE at 12 months in the intervention groups was 0.90 lower (0.12 to 1.68 lower)	-	156 (1 study)	⊕⊕⊕⊕ low 1,2	Evidence of a small effect on the MMSE favouring glibenclamide (glyburide) at 12 months.
Incidence of MCI	No evidence identified.					
Incidence of dementia	No evidence identified.					
Adverse events (Hypoglycaemia)	No evidence identified.					
Mortality	No evidence identified.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ Abbatecola et al (2006) has an unclear risk of bias due to no description on the random sequence generation, allocation concealment, blinding of participants and personnel, and selective reporting.

² Single study with a small sample size: 156 patients.

Summary of findings 2. Intensive glycaemic control compared to standard glycaemic control for Type 2 diabetes

Intense glycaemic control compared to standard glycaemic control for Type 2 diabetes

Patient or population: patients with Type 2 diabetes

Settings: general population

Intervention: intense glycaemic control

Comparison: standard glycaemic control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard glycaemic control	Intense glycaemic control				
Global cognitive function (defined as reduction of at least 3 points in MMSE)	164 per 1000	160 per 1000 (144 to 177)	RR 0.98 (0.88 to 1.08)	11,140 (1 study)	⊕⊕⊕⊖ moderate ¹	Evidence of no significant difference between intensive and standard glycaemic control.
Global cognitive function measured by MMSE at 40 months		The mean general cognitive function measured by MMSE at 40 months in the intervention groups was 0.01 lower (0.18 lower to 0.16 higher)	-	2794 (1 study)	⊕⊕⊕⊖ moderate ²	Evidence of no significant difference between intensive and standard glycaemic control.
Incidence of MCI	No evidence identified.					
Incidence of dementia (defined as dementia according to DSM-IV)	9 per 1000	11 per 1000 (7 to 16)	RR 1.27 (0.87 to 1.85)	11,140 (1 study)	⊕⊕⊖⊖ low ^{1,3}	Evidence of no significant difference between intensive and standard glycaemic control.
Adverse events (Hypoglycaemia)	17 per 1000	36 per 1000 (25 to 52)	RR 2.18 (1.52 to 3.14)	12,931 (2 studies)	⊕⊕⊖⊖ low ^{1,4}	Evidence of a significantly higher incidence of hypoglycaemic events for intensive

						sive glycaemic control compared with standard glycaemic control.
Mortality	81 per 1000	81 per 1000 (64 to 102)	RR 1.0 (0.79 to 1.26)	15,888 (3 studies)	⊕⊕⊕⊕ moderate ¹	Evidence of no significant difference between intensive and standard glycaemic control.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ The ADVANCE study has an unclear risk of bias due to no description in the random sequence generation, allocation concealment, and blinding of participants and personnel.

² Launer et al has a high risk of bias in the blinding of participants and personnel and an unclear risk of bias due to no description in the blinding of outcome assessors and incomplete outcome data.

³ Event rate low (61 in the intervention group and 48 in the control group).

⁴ Wide 95% confidence interval around the pooled estimate of effect.

Summary of findings 3. Rosiglitazone plus metformin compared to glibenclamide (glyburide) plus metformin for Type 2 diabetes

Rosiglitazone plus metformin compared to glibenclamide (glyburide) plus metformin for Type 2 diabetes

Patient or population: patients with Type 2 diabetes

Settings: general population

Intervention: rosiglitazone plus metformin

Comparison: glibenclamide (glyburide) plus metformin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Glibenclamide (glyburide) plus metformin	Rosiglitazone plus metformin				
Global cognitive function	No evidence identified.					

Incidence of MCI	No evidence identified.
Incidence of dementia	No evidence identified.
Adverse events (Hypoglycaemia)	No evidence identified.
Mortality	No evidence identified.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

BACKGROUND

According to the World Health Organization (WHO), dementia affects 47 million people worldwide. Every year there are 9.9 million new cases. The world total is expected to increase to 75.6 million in 2030 and 135.5 million in 2050 (WHO 2017). Also according to the WHO, 422 million people worldwide have diabetes, a number likely to more than double in the next 20 years (WHO 2016b). Both dementia and diabetes mellitus represent major public health problems since both are associated with long-term disability.

Description of the condition

Diabetes mellitus can be divided into two major categories. Type 1 diabetes mellitus is an autoimmune disorder in which the insulin-producing beta cells in the pancreas are destroyed. It typically begins in childhood or early adulthood (Atkinson 1994), although it can occur in adults as well (ADA 2017a). Type 2 diabetes mellitus is characterised by insulin resistance in peripheral tissues and progressive dysfunction of beta pancreatic cells (Kahn 2014). It usually affects adults, its prevalence increasing with age.

Diabetes may be diagnosed based either on the fasting plasma glucose (FPG) or the plasma glucose two hours after a 75 g oral glucose tolerance test (2-h PG) — the plasma glucose criteria; or on the level of glycated haemoglobin in the blood — the HbA1c criteria (ADA 2017a).

There are a number of serious complications associated with diabetes. These have traditionally been divided into microvascular complications (retinopathy, neuropathy, and nephropathy) and macrovascular complications (cardiovascular and cerebrovascular disease) (Wright 2016).

Cognition is a term used to describe a set of higher cerebral functions, including memory, language, executive function, attention, perception and social behaviour. Dementia is a condition of cognitive impairment, usually progressive and irreversible, which involves a significant decline from a previous level of function and which interferes with independence in everyday activities (DSM-5 2013). The greatest risk factor for dementia is increasing age. The most common diseases that lead to dementia are Alzheimer's disease (AD) and cerebrovascular diseases (Morris 2003).

In recent years, important epidemiological evidence has been gathered regarding the relationship between diabetes, cognitive dysfunction and dementia. No evidence of a substantial long-term decline in cognitive function has been found in a large group of patients with Type 1 diabetes followed for an average of 18 years (DCCT/EDIC 2007), although this remains somewhat controversial (Kodl 2008). Cognitive changes have been described in Type 2 diabetes, affecting mainly learning and memory, mental flexibility and mental speed (Kodl 2008). People with Type 2 diabetes mellitus have been reported to have a risk of developing dementia 1.5 to 2 times higher than people without diabetes (Ott 1999; Gregg 2000; Cukierman 2005). A more recent meta-analysis by Cheng 2012 found the relative risk of developing dementia in people with diabetes versus those without diabetes to be 1.46 for dementia due to Alzheimer's disease and 2.48 for vascular dementia. Diabetes mellitus and pre-diabetes have also been found to accelerate the rate of progression from mild cognitive impairment to dementia (Xu 2010). Patients with Type 2 diabetes and established dementia

have been found to be less likely to receive adequate diabetic care compared with those who have diabetes alone (Bunn 2014). The relationship between diabetes and dementia is likely to be complex and multifactorial.

Patients with Type 2 diabetes mellitus often have other cardiovascular risk factors and conditions, including high blood pressure, dyslipidaemia, cardiovascular disease, and cerebrovascular diseases that may contribute to cognitive impairment (Prince 1996; Kilander 1998; Rockwood 2002). Macrovascular disease, both peripheral and cerebral, is associated with dementia risk in patients with Type 2 diabetes mellitus (Bruce 2008). Cerebrovascular disease underlies vascular and mixed dementia and it has also been suggested that it triggers a series of events that lead to Alzheimer's disease (De la Torre 2000; Kalaria 2000; Shi 2000).

Patients with diabetes may develop microvascular disease, manifested as diabetic nephropathy and retinopathy. Albuminuria, an indicator of nephropathy, is associated with accelerated cognitive impairment (Barzilay 2013). It has also been shown that diabetic retinopathy is associated with dementia risk in patients with Type 2 diabetes mellitus (Exalto 2014).

Diabetes has a bidirectional association with depression, which is associated with dementia (Hugo 2014; Tabák 2014).

Insulin receptors are widely distributed in the brain, especially on neurons in areas concerned with memory and learning, such as the hippocampus and parts of the cerebral cortex (Wickelgren 1998). It is possible that insulin disorders may affect the utilisation of glucose in these areas. Type 2 diabetes also causes extensive disturbances in brain insulin and insulin-like growth factor signalling mechanisms, which could promote molecular, biochemical, and histopathological lesions in AD (de la Monte 2008).

Description of the intervention

Treatment for a patient with Type 2 diabetes should be individualised, taking into account the patient's characteristics and comorbidities (NICE 2016; AACE/ACE 2017; ADA 2017b). International clinical practice guidelines (CPGs) and consensus standards vary, but all agree that the first line of treatment should include lifestyle changes, such as exercise and weight loss. Counselling may be provided to support these goals (NICE 2016; AACE/ACE 2017; ADA 2017c). Additional pharmacological treatment may also be offered at the time of diagnosis (AACE/ACE 2017); and is recommended if lifestyle recommendations do not achieve glycaemic goals (NICE 2016; ADA 2017b).

There are many different drugs available to treat Type 2 diabetes, including metformin, sulphonylureas, thiazolidinediones, dipeptidyl-peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists and insulin (NICE 2016; AACE/ACE 2017; ADA 2017b). Depending on the level of HbA1c, treatment may start with a single agent, commonly metformin, or a combination of drugs. The treatment becomes more complex if satisfactory glycaemic control is not achieved over time. Important factors influencing the choice of drug treatment relate to the overall health condition of the patient, especially considering the risk of hypoglycaemia, comorbidities, functional status, remaining life

expectancy, renal disease, and macrovascular complications (NICE 2016; AACE/ACE 2017; ADA 2017b); and the presence and degree of cognitive impairment or dementia (ADA 2017d).

In recent years, intensive treatment strategies have been proposed to reduce the risk of micro- and macrovascular complications. However, the more intensive the treatment, the greater the risk of adverse effects such as hypoglycaemia and higher mortality. Therefore, intensive treatment might be not suitable in those at high risk of treatment complications (ADA 2017d; ADA 2017e).

How the intervention might work

Different drug treatments may have differential effects on dementia risk due to different actions on pathophysiological processes at the molecular level or different effects on other risk factors for cognitive decline. Hyperglycaemia is a risk factor for dementia (Crane 2013). Haemoglobin A1c levels reflect average glycaemia over several months. High levels have a strong predictive value for general diabetic complications and are related to the risk of developing cognitive impairment (Yaffe 2006). Hence, glycaemic control seems to be related to cognitive dysfunction in patients with Type 2 diabetes and tight glycaemic control may lower the risk of cognitive decline and dementia. On the other hand severe hypoglycaemia, which can be caused by pharmacological treatment of diabetes, may have permanent neurological consequences which may accelerate dementia. There are studies demonstrating that episodes of serious hypoglycaemia which require hospitalisation or visits to the emergency room are associated with a higher risk of dementia, and a greater number of episodes increases the risk (Whitmer 2009).

Why it is important to do this review

There is a very high level of interest in any interventions which could prevent or delay the onset of dementia. Since diabetes is a risk factor for dementia and is very common in the older population at risk of dementia, its treatment offers considerable potential for prevention. This review aims to identify and synthesise high-quality evidence to determine whether different management strategies for Type 2 diabetes have any effect on cognitive function and the incidence of dementia. Given the prevalence of both conditions, even small effects of a particular management strategy could have consequences for public health.

OBJECTIVES

To assess the effects of different strategies for managing Type 2 diabetes mellitus on cognitive function and the incidence of dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of treatments approved by international clinical practice guidelines for Type 2 diabetes in which objective measures of participants' cognitive function were made at baseline and after treatment.

Types of participants

We included people over 18 years old suffering from Type 2 diabetes diagnosed by accepted international criteria — ADA Diagnosis 2016 — and treated in the community. Type 1 diabetes patients were excluded. There were no exclusion criteria based on comorbidity.

Types of interventions

We included any treatment approved by international guidelines for Type 2 diabetes given for a minimum of 12 weeks. The following types of interventions were acceptable: diet, exercise, any orally administered or injected antidiabetic drug at any dose (ADA 2016). Comparator interventions could be treatment as usual, placebo, or an alternative active treatment. We included studies comparing different goals of treatment (intensive or conventional treatment).

Types of outcome measures

- Cognitive function measured by validated neuropsychological tests. These may be neuropsychological test batteries, multi-domain or single domain cognitive tests. We sought data on global cognitive function (our most important cognitive outcome) and the specific cognitive subdomains of executive function, processing speed, semantic memory, verbal fluency, working memory and episodic memory.
- Incidence of mild cognitive impairment (MCI) identified using explicit criteria, including Petersen criteria or revised Petersen criteria (Petersen 1999; Petersen 2004; Winblad 2004); any of the 16 different definitions of MCI described by Matthews 2008; or a Clinical Dementia Rating of 0.5 (Morris 1993).
- Incidence of dementia or any subtype of dementia diagnosed by validated criteria, including National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS ADRDA) criteria (McKhann 1984), the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (DSM-III-R 1987; DSM-IV 2004), the International Classification of Diseases (ICD) (ICD-10), and the National Institute on Aging/Alzheimer Association (NIA-AA) criteria for dementia (McKhann 2011).
- Adverse events: hypoglycaemic episodes.
- Mortality.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialized Register, on 15 October 2016. The search terms used were: diabetic OR diabetes OR "type 2" OR "type II".

ALOIS is maintained by the Information Specialists of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS;
2. Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of

- Clinical Trials and the Netherlands National Trials Register, plus others);
- Quarterly search of the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
 - Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'Methods used in reviews' section within the editorial information about the [Dementia and Cognitive Improvement Group](#).

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up to date and as comprehensive as possible. The search strategies used can be seen in [Appendix 1](#).

Searches carried out in the previous versions of the review can be viewed in [Appendix 2](#).

To date, this review has had a total of five searches (2008, 2011, 2014, 2015 and 2016).

Data collection and analysis

We tried to contact the trial investigators whenever data were missing, unclear, or if we believed we had detected a possible error in the published data. If this was unsuccessful, we described the uncertainties. We did not impute any missing data.

Selection of studies

Two authors (AA, MG) independently assessed the retrieved titles and abstracts to identify potentially eligible studies, for which we obtained the full paper. A third author (GM) resolved disagreements between the two authors. Two authors (AA, MG) independently assessed the full manuscripts against the inclusion criteria. Where necessary, a third author (GM) acted as arbitrator to resolve disagreements that the two review authors were unable to resolve through discussion. If a study did not present all relevant data, we contacted the authors directly to request further information. If the same data set was presented in more than one paper, we included the paper with the largest number of patients or with the most informative data.

Data extraction and management

Two review authors (RV, GM), working independently, extracted trial information using a standardised data extraction form ([Appendix 3](#)). Where possible we extracted, as a minimum, the following information.

Participant characteristics

- Gender.
- Age (range, median, mean).
- Education (level and years of education).
- Baseline cognitive function.
- Cognitive diagnostic status.
- Duration of cognitive symptoms, if any.

- Ethnicity.

Intervention characteristics

- Description of the intervention.
- Description of the control condition.
- Frequency and dose of treatment.
- Duration of treatment.

Methodological characteristics

- Trial design (individual or cluster randomisation; parallel-group, factorial or cross-over design).
- Number of participants.
- Outcome measures used.
- Duration of follow-up as measured from randomisation.
- Duration of follow-up as measured from end of treatment.
- Source of financial support.
- Publication status.

For dichotomous outcomes, we extracted from each trial the number of participants with each outcome at end of treatment. For continuous outcomes, we extracted the number of participants and the mean and standard deviation (SD) of the change from baseline for each outcome at end of treatment. If change from baseline data were not available, we extracted the mean and standard deviation of the final values from each group. The baseline assessment is defined as the latest available assessment prior to randomisation, but no longer than two months before.

We included only one outcome from a study in an analysis for each cognitive subdomain. If a study included more than one scale measuring a single cognitive subdomain, then we favoured the scale which was included in the most studies for that comparison. If this did not identify a preferred scale, then we favoured the scale highest in a hierarchy of scales based on frequency of use in a set of 12 Cochrane Reviews on modifiable risk factors for dementia (see [Appendix 3](#)). If study authors had derived composite cognitive outcomes, then we also extracted and described these.

Assessment of risk of bias in included studies

Two reviewers of the author team (RV, GM) independently assessed the risk of bias in each of the included trials, using Cochrane's 'Risk of bias' tool ([Higgins 2011](#)). Disagreements were resolved by discussion until consensus was reached. We assessed the risk of bias potentially introduced by the following features of study design: sequence generation, allocation concealment, blinding of participants and healthcare professionals, blinding of outcome assessors, selective outcome reporting, and incomplete outcome data.

Measures of treatment effect

We estimated effects of diabetes treatment by using risk ratios (RRs) for dichotomous variables and mean differences (MDs) or standardised mean differences (SMDs) for continuous variables, along with their corresponding 95% confidence intervals (CIs). We calculated SMDs when studies used different instruments to measure the same variable.

Unit of analysis issues

We used individual study participants in each trial arm as the unit of analysis.

Dealing with missing data

We did not numerically impute missing values where participants were lost to follow-up from either group. For continuous outcomes, we analysed the data provided by study authors. Missing data in the individual trials may put the study estimates of effects at a high risk of bias and may lower the overall quality of the evidence according to the GRADE assessment. We included the information about the missing data in our 'Risk of bias' assessments.

Assessment of heterogeneity

We assessed differences between the included studies in the types of participants, interventions or control used before deciding whether to pool data. No subgroup analyses were planned. We assessed heterogeneity between studies using the Chi² test (with a significance level set at $P < 0.10$) and the I² statistic, which calculates the percentage of variability due to heterogeneity rather than to chance, with I² values over 50% suggesting substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

We did not find enough trials to be able to explore reporting biases and other biases related to small-study effects.

Data synthesis

We pooled data from studies only if we considered them to be sufficiently similar in terms of participants, interventions, duration and outcomes and if I² was less than 75%. Additionally, we used a fixed-effect model if we considered all studies in a meta-analysis to be estimating the same underlying effect. If we thought this was not the case due to clinical or statistical heterogeneity, then we used a random-effects model.

Summary of findings

We used the principles of the GRADE system to assess the quality of the body of evidence associated with each outcome. We

constructed a 'Summary of findings' table for each comparison using GRADE profiler software (GRADEpro 2008). The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Evaluation of the quality of a body of evidence considers within-study risk of bias, directness of the evidence, heterogeneity in the data, precision of effect estimates and additional considerations (including risk of publication bias) (Guyatt 2008).

Two review authors (GM and RV) independently assessed the quality of the body of evidence on the following outcomes: global cognitive function, incidence of MCI, incidence of dementia, adverse effects (hypoglycaemia) and mortality.

Subgroup analysis and investigation of heterogeneity

We were not able to include enough trials to conduct subgroup analyses.

Sensitivity analysis

We did not conduct any sensitivity analyses.

RESULTS

Description of studies

Details of all included and excluded studies are provided in the [Characteristics of included studies](#) and [Characteristics of excluded studies](#) tables.

Results of the search

Database searches conducted for this review identified a total of 4944 results. After de-duplication and first assessments by the information specialist for the Cochrane Dementia and Cognitive Improvement Group, and a further first assessment by the author team (AA and MG), a total of 34 articles were reviewed in full text. Two reviewers (AA, MG) independently assessed them for inclusion or exclusion. A third reviewer (GM) resolved discrepancies. See [Figure 1](#).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

For the current update of this Cochrane Review, we identified seven new included studies (Abbatecola 2006; Ryan 2006; ADVANCE 2008; Launer 2011; Araki 2012; Guo 2014; Zimring 2016). Additionally, we excluded the five studies that were included in the 2008 version of this review (see Excluded studies).

Study designs

All seven included studies were individually randomised, parallel group randomised controlled trials (RCTs). Two studies had a 2 × 2 factorial design (ADVANCE 2008; Launer 2011). The other studies had single intervention and control groups (Abbatecola 2006; Ryan 2006; Araki 2012; Guo 2014; Zimring 2016).

Settings

One trial was conducted in a single academic outpatient centre in Italy (Abbatecola 2006); one trial was conducted in 215 clinical centres in 20 different countries in Asia, Australasia, Europe, and North America (ADVANCE 2008); one trial was conducted in outpatient clinics at 39 hospitals in Japan (Araki 2012); one trial was conducted in 52 outpatient clinics in North America (Launer 2011); one study was conducted in 20 Veteran Affairs Medical Centers in the USA (Zimring 2016); and two trials provided no information on setting (Ryan 2006; Guo 2014).

Participants

Abbatecola 2006 included 156 treatment-naïve Type 2 diabetic participants aged between 60 and 78 years. The ADVANCE 2008 study included 11,140 participants who had their first diagnosis

of Type 2 diabetes at age 30 years or older, were age 55 years or older at entry (mean 66 ± 6 years), and were at substantial risk of vascular events. Araki 2012 included 1173 Type 2 diabetic participants aged over 65 years who also had other cardiovascular risk factors. Launer 2011 included 1977 participants with Type 2 diabetes, a high HbA1c concentration (> 7.5%, > 58 mmol/mol) and a high risk for cardiovascular disease events. Guo 2014 included 144 treatment-naïve Type 2 diabetic participants aged between 40 and 65 years who also had depression diagnosed according to DSM-IV 2004 criteria. Ryan 2006 included 145 participants with Type 2 diabetes who were treated with metformin. Finally, Zimring 2016 included 1791 participants older than 41 years (mean 60 years), who were non-responsive to a maximum dose of at least one oral agent or daily insulin injections, or both.

Interventions

One study compared a variable dose of metformin (initially 0.5 g twice a day) to placebo over 24 weeks (Guo 2014).

Two studies compared two different antidiabetic drugs.

- Abbatecola 2006 compared repaglinide (initially 1 mg twice a day) to glibenclamide (glyburide) (initially 2.5 mg twice a day) over 12 months. (Glibenclamide is known as glyburide in the United States).
- Ryan 2006 compared rosiglitazone (initially 4.0 mg once a day) plus metformin to glibenclamide (glyburide) (initially 2.5 mg twice a day) plus metformin over 24 weeks (Ryan 2006).

Four studies compared standard and intensive regimes for diabetes control.

- [Launer 2011](#) randomised the participants to receive 40 months of either intensive glycaemic treatment with an HbA1c target of less than 6.0% or standard glycaemic control with an HbA1c target of 7.0% to 7.9%. All participants received diabetes education, glucose-monitoring equipment, and antidiabetic medications. Participants in the intensive glycaemic group were started on two or more classes of agents. Doses were intensified or a new medication class was added monthly if HbA1c levels were 6% or more, or if more than 50% of premeal or postmeal capillary glucose readings were higher than 5.6 mmol/L (100 mg/dL). Standard glycaemic therapy was intensified whenever HbA1c was 8% or above, or more than 50% of capillary glucose readings were higher than 7.8 mmol/L (140 mg/dL). Antihyperglycaemic drugs that promoted hypoglycaemia (i.e. insulin or insulin secretagogues) were reduced if HbA1c was persistently lowered to less than 7%. All drug combinations from a standard formulary were permitted; specific drugs were reduced only for side effects or contraindications. In addition, the patients were randomly assigned to receive either intensive blood pressure-lowering treatment (systolic blood pressure target < 120 mmHg) or standard treatment (systolic blood pressure target < 140 mmHg); and to receive fenofibrate or placebo.
- The [ADVANCE 2008](#) study compared an intensive glucose control regime including gliclazide (modified release, 30 mg to 120 mg daily) plus other treatments at physicians' discretion versus a standard control group, whose treatment could not include gliclazide, for a median follow-up of five years. Eligible participants were also randomised to perindopril-indapamide or placebo. Whenever required, other classes of blood pressure-lowering drugs were prescribed at the discretion of the responsible clinician.
- [Araki 2012](#) randomised participants to either an intensive regime of treatment for diabetes, hypertension and dyslipidaemia or treatment as usual over six years. The diabetes treatment target for the intensive treatment regime was HbA1c lower than 6.9%. (Treatment targets for the other factors are shown in the [Characteristics of included studies](#) table.)
- [Zimring 2016](#) randomised participants to intensive or standard therapy and followed them up for five years. Both intensive and standard therapy groups were divided according to participants' BMI. Those with a BMI of 27 or more were started on two oral agents, rosiglitazone plus metformin; those with a BMI of less than 27 were started on rosiglitazone plus glimepiride. The participants in the intensive therapy treatment started on maximal doses and, before any change in oral medications, insulin was added for patients who did not achieve a glycated haemoglobin level of lower than 6%. In the standard therapy group, the oral treatment was started at half the maximal doses and, before any change in oral medications, insulin was added for participants who did not achieve a glycated haemoglobin level of lower than 9%.

Outcomes

Four studies measured global cognitive function using the Mini-Mental State Examination (MMSE) ([Abbatecola 2006](#); [ADVANCE 2008](#); [Launer 2011](#); [Araki 2012](#)). The [ADVANCE 2008](#) study reported

this only as the number of patients who had declined by 3 or more MMSE points from baseline.

Four studies used a variety of cognitive subdomain tests. We extracted outcomes according to the methods specified in [Data extraction and management](#) (above).

Episodic memory was measured by both [Ryan 2006](#) and [Launer 2011](#) using the Rey Auditory Verbal Learning Test (RAVLT). Executive function was evaluated by [Launer 2011](#) using the Stroop test. Speed of processing was evaluated by [Ryan 2006](#) and [Launer 2011](#) using the Digit Symbol Substitution Test. Working memory was evaluated by [Ryan 2006](#) using the Spatial Working Memory Test. [Guo 2014](#) measured episodic and working memory using subtests of the Wechsler Memory Scale-Revised (WMS-R), and [Zimring 2016](#) measured executive function using the Trail Making Test-B (TMT-B), speed of processing using Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and working memory using Digit-Span Forwards and Backwards, but they did not present extractable data.

Two studies also reported composite cognitive outcomes. [Abbatecola 2006](#) reported a cognition composite score of attention and executive functions. [Ryan 2006](#) reported composite outcomes in three domains which they called 1) working memory, 2) learning ability and 3) cognitive efficiency. The details of the composite outcomes are given in the [Characteristics of included studies](#) table.

No study reported the incidence of MCI.

Only one study reported the incidence of dementia (using DSM-IV criteria) ([ADVANCE 2008](#)).

Two studies reported adverse events. Both of them reported specifically on hypoglycaemic episodes ([ADVANCE 2008](#); [Zimring 2016](#)).

Three studies reported mortality ([ADVANCE 2008](#); [Launer 2011](#); [Zimring 2016](#)).

Excluded studies

We excluded three studies because they studied the effect of different diabetic treatments on quality of life using questionnaires that included the respondents' subjective impressions of cognitive function ([Testa 1998](#); [Tovi 1998](#); [UKPDS 1999](#)), instead of using objective measures. One study was excluded because the participants had pre-diabetes (dysglycaemia) ([Cukierman-Yaffe 2014](#)). We excluded [Naor 1997](#), which compared the effect of intensive inpatient diabetic therapy with unchanged regular diabetic therapy on cognitive function over a short period of time (six weeks). A number of studies were excluded because the interventions were not eligible: these were ginseng ([Sotaniemi 1995](#)), vitamin E ([Vijayakumar 2011](#)), dietary nitrate supplementation ([Gilchrist 2014](#)), Sancaijiangtang ([Qiang 2015](#)), and telemedicine ([Luchsinger 2011](#)).

Risk of bias in included studies

We considered none of the included studies to have an overall low risk of bias ([Characteristics of included studies](#); [Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abbatecola 2006	?	?	?	?	+	+	?	+
ADVANCE 2008	+	+	?	?	+	+	+	+
Araki 2012	?	?	?	?	?	+	+	+
Guo 2014	+	?	?	?	?	-	-	+
Launer 2011	+	+	-	-	?	?	+	+
Ryan 2006	+	?	?	?	+	+	?	+
Zimring 2016	?	?	?	?	?	?	+	?

Allocation

Three studies did not clearly report the method used for random sequence generation and we judged them to have an unclear risk of bias in this domain (Abbatecola 2006; Araki 2012; Zimring 2016). We judged two studies to have a low risk of bias on the allocation concealment item because the authors described use of a computer-generated unique randomisation sequence (ADVANCE

2008), and implemented the randomisation via secure access (Launer 2011). The other five studies did not give any description of how allocation was concealed (Abbatecola 2006; Ryan 2006; Araki 2012; Guo 2014; Zimring 2016).

Blinding

One study was explicitly open label and we judged it to have a high risk of performance and detection bias (Launer 2011). None of the other studies clearly described blinding of patients and personnel and we judged them all to be at unclear risk of performance bias. Three studies were also at unclear risk of detection bias due to a lack of information about blinding of outcome assessors (Araki 2012; Guo 2014; Zimering 2016). Three studies described an adequate method for blinding the outcome assessors and we considered them to be at low risk of detection bias (Abbatecola 2006; Ryan 2006; ADVANCE 2008).

Incomplete outcome data

We considered five studies to have a low risk of attrition bias (Abbatecola 2006; Ryan 2006; ADVANCE 2008; Launer 2011; Araki 2012). We considered Guo 2014 to have a high risk of attrition bias because 19.4% of patients were lost to follow-up; the reasons for these post-randomisation withdrawals were not reported. We considered Zimering 2016 to be at unclear risk of attrition bias due to a lack of information about the number of patients lost before final analysis and no description of how losses to follow-up were handled.

Selective reporting

We considered four studies to have a low risk of reporting bias (ADVANCE 2008; Launer 2011; Araki 2012; Zimering 2016). Two studies did not report the existence of a protocol in which the outcomes were specified, and so we assigned them an unclear risk of bias regarding selective outcome reporting (Abbatecola 2006; Ryan 2006). In one study no protocol was identified and only results at 12 weeks were reported although the Methods section described a follow-up time of 24 weeks; we considered this to indicate a high risk of bias (Guo 2014).

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Glibenclamide (glyburide) compared to Repaglinide for Type 2 diabetes; **Summary of findings 2** Intensive glycaemic control compared to standard glycaemic control for Type 2 diabetes; **Summary of findings 3** Rosiglitazone plus metformin compared to glibenclamide (glyburide) plus metformin for Type 2 diabetes

See 'Summary of findings' tables for the comparisons of: 1) glibenclamide (glyburide) versus repaglinide; 2) intensive glycaemic control versus standard glycaemic control; and 3) rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin.

There is no 'Summary of findings' table for the comparison of metformin with placebo because we were unable to extract data from the study concerned (Guo 2014).

We were unable to extract any efficacy data from two of the seven included studies. Araki 2012 did not report the MMSE scores at the end of the follow-up; the authors were contacted twice to request the data for inclusion in this systematic review, but no response was received. It was not possible to extract the data we needed from Guo

2014 because the results were reported only in an ANOVA format and no data could be extracted from the figures. Similarly, the authors were contacted twice to request the data, but no response was received. Zimering 2016 did not report measures of dispersion (e.g. standard deviation) for its cognitive outcomes and so we were not able to include this efficacy data in the meta-analyses. We were able to extract data related to safety from only three studies of the seven studies included (ADVANCE 2008; Launer 2011; Zimering 2016).

Comparison 1: glibenclamide (glyburide) versus repaglinide

One study with 156 participants made this comparison (Abbatecola 2006).

Outcome: global cognitive function measured with MMSE at 12 months

There was low-quality evidence from one study of a small advantage on global cognitive function measured with the MMSE for glibenclamide (glyburide) over repaglinide after 12 months of treatment (MD -0.90, 95% CI -1.68 to -0.12; 1 study; n = 156; low-quality evidence, downgraded due to risk of bias and imprecision) (Analysis 1.1).

Outcome: executive function

No data were reported on executive function.

Outcome: speed of processing

No data were reported on speed of processing.

Outcome: semantic memory

No data were reported on semantic memory.

Outcome: verbal fluency

No data were reported on verbal fluency.

Outcome: working memory

No data were reported on working memory.

Outcome: episodic memory

No data were reported on episodic memory.

Outcome: other cognitive outcomes

Abbatecola 2006 also reported a cognition composite score of attention and executive functions. It consisted of the sum of the squared z-scores of TMT-A, TMT-B, DIFF B-A, DSP-Forward, DSP-Backward, and Verbal Fluency. There was no difference between groups on this outcome (MD 0.00, 95% CI -0.01 to 0.01; 1 study; n = 156; low-quality evidence, downgraded due to risk of bias and imprecision) (Analysis 1.2).

Outcome: incidence of MCI

No data were reported on incidence of MCI.

Outcome: incidence of dementia or any subtype of dementia

No data were reported on incidence of dementia or any subtype of dementia.

Outcome: adverse events

No data were reported on adverse events.

Outcome: mortality

No data were reported on mortality.

Comparison 2: intensive glycaemic control versus standard glycaemic control

Four studies with 16,081 participants made this comparison. However, we were not able to include any data from [Araki 2012](#) (1173 participants).

Outcome: global cognitive function

There was no difference between the intensive glycaemic control group and the standard glycaemic control group on global cognitive function measured with the MMSE at 40 months (MD -0.00, 95% CI -0.08 to 0.07; 1 study; n = 2794; moderate-quality evidence, downgraded due to risk of bias) ([Launer 2011](#)) ([Analysis 2.1](#)).

Outcome: global cognitive function (dichotomous)

[ADVANCE 2008](#) reported MMSE results only as the number of participants who had declined by 3 or more points from baseline. There was no difference between the intensive glycaemic control group and the standard glycaemic control group on this outcome at five years (RR 0.98, 95% CI 0.88 to 1.08; 1 study; n = 11,140; moderate-quality evidence, downgraded due to risk of bias) ([Analysis 2.2](#)).

Outcome: executive function

There was no clear evidence of a difference between the intensive glycaemic control group and the standard glycaemic control group on executive function measured with the Stroop test at 40 months (MD -0.61, 95% CI -1.62 to 0.40; 1 study; n = 2794; moderate-quality evidence, downgraded due to risk of bias) ([Launer 2011](#)) ([Analysis 2.3](#)).

[Zimering 2016](#) reported the mean change after five years on executive function measured with TMT-B, but did not report any measure of dispersion of the data (e.g. standard deviation or standard error) and so we were not able to include this in a meta-analysis. The authors reported no evidence of a difference between the intensive glycaemic control group and the standard glycaemic control group.

Outcome: speed of processing

There was no clear evidence of a difference between the intensive glycaemic control group and the standard glycaemic control group on speed of processing measured by DSST at 40 months (MD 0.32, 95% CI -0.28 to 0.92; 1 study; n = 2794; moderate-quality evidence, downgraded due to risk of bias) ([Launer 2011](#)) ([Analysis 2.5](#)).

[Zimering 2016](#) reported the mean change after five years on speed of processing measured with the DSST, but did not report any measure of dispersion of the data and so we were not able to include this in a meta-analysis. The authors reported no evidence of a difference between the intensive glycaemic control group and the standard glycaemic control group.

Outcome: semantic memory

No data were reported on semantic memory.

Outcome: verbal fluency

No data were reported on verbal fluency.

Outcome: working memory

[Zimering 2016](#) reported the mean change after five years on working memory measured by digit span, but did not report any measure of dispersion of the data. The authors reported no evidence of a difference between the intensive glycaemic control group and the standard glycaemic control group.

Outcome: episodic memory

There was no difference between the intensive glycaemic control group and the standard glycaemic control group on episodic memory measured with the RAVLT at 40 months (MD -0.01, 95% CI -0.14 to 0.12; 1 study; n = 2794; moderate-quality evidence, downgraded due to risk of bias) ([Launer 2011](#)) ([Analysis 2.4](#)).

Outcome: incidence of MCI

No data were reported on incidence of MCI.

Outcome: incidence of dementia or any subtype of dementia

One study reported the incidence of dementia ([ADVANCE 2008](#)). The result was imprecise and did not show a statistically significant difference between the intensive glycaemic control group compared with the standard glycaemic control group after five years (RR 1.27, 95% CI 0.87 to 1.85; 1 study; n = 11,140; low-quality evidence, downgraded due to risk of bias and imprecision) ([Analysis 2.6](#)).

Outcome: adverse events; hypoglycaemia

[ADVANCE 2008](#) defined a severe hypoglycaemic episode as a participant with transient dysfunction of the central nervous system, unable to treat themselves and requiring help from another person. [Zimering 2016](#) also reported severe hypoglycaemic episodes defined as death, hospitalisation, disability or incapacity, or other important event requiring medical intervention/treatment due to a hypoglycaemic episode. There was moderate-quality evidence from two studies of a greater risk of at least one severe hypoglycaemic episode for the intensive glycaemic control group over the standard glycaemic control group after five years of treatment (RR 2.18, 95% CI 1.52 to 3.14; 2 studies; n = 12,827; moderate-quality evidence, downgraded due to risk of bias) ([Analysis 2.7](#)).

Outcome: mortality

There was no difference in all-cause mortality between the intensive glycaemic control group and the standard glycaemic control group, but the result was imprecise and compatible with a small increase in mortality in either group (RR 0.99, 95% CI 0.87 to 1.13, 3 studies, n = 15,888; low-quality evidence, downgraded due to risk of bias and imprecision) ([Analysis 2.8](#)).

Comparison 3: rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin

One study with 145 participants made this comparison ([Ryan 2006](#)).

Outcome: global cognitive function

No data were reported on global cognitive function.

Outcome: executive function

No data were reported on executive function.

Outcome: speed of processing

There was no clear evidence of a difference between rosiglitazone plus metformin and glibenclamide (glyburide) plus metformin in cognitive speed measured with the DSST after 24 weeks of treatment (MD -0.20, 95% CI -0.50 to 0.10; 1 study; n = 136; low-quality evidence, downgraded due to risk of bias and imprecision) (Ryan 2006) (Analysis 3.9).

Outcome: semantic memory

No data were reported on semantic memory.

Outcome: verbal fluency

No data were reported on verbal fluency.

Outcome: working memory

There was no difference between rosiglitazone plus metformin and glibenclamide (glyburide) plus metformin in working memory measured with the Spatial Working Memory Test after 24 weeks of treatment (MD 0.40, 95% CI -0.24 to 1.04; 1 study; n = 136; low-quality evidence, downgraded due to risk of bias and imprecision) (Ryan 2006) (Analysis 3.6).

Outcome: episodic memory

There was low-quality evidence from Ryan 2006 of a small advantage for rosiglitazone plus metformin over glibenclamide (glyburide) plus metformin on episodic memory measured with the RAVLT (immediate) after 24 weeks of treatment (MD -1.40, 95% CI -1.70 to -1.10; 1 study; n = 136; low-quality evidence, downgraded due to risk of bias and imprecision) (Analysis 3.10).

Outcome: other cognitive outcomes

There was no difference between rosiglitazone plus metformin and glibenclamide (glyburide) plus metformin on the study authors' composite outcomes of working memory, learning ability and cognitive efficiency (defined in Characteristics of included studies table) (Analysis 3.1; Analysis 3.2; Analysis 3.3). After 24 weeks, there were small numerical advantages for rosiglitazone plus metformin over glibenclamide (glyburide) plus metformin on the CANTAB items of Paired Associates Learning, Pattern Recognition Memory and Rapid Visual Information Processing and a small numerical advantage for glibenclamide (glyburide) plus metformin over rosiglitazone plus metformin on the CANTAB item Reaction Time (Analysis 3.4; Analysis 3.5; Analysis 3.7; Analysis 3.8 respectively). We considered all these results to be low-quality evidence, downgraded due to risk of bias and imprecision.

Outcome: incidence of MCI

No data were reported on the incidence of MCI.

Outcome: incidence of dementia or any subtype of dementia

No data were reported on the incidence of dementia.

Outcome: adverse events

No data were reported on hypoglycaemic events.

Outcome: mortality

No data were reported on mortality.

Comparison 4: Metformin versus placebo

One study with 72 participants made this comparison in Type 2 diabetes participants with depression; however, we were unable to extract the data because the results were reported only in an ANOVA format and no data could be extracted from the figures (Guo 2014)

DISCUSSION

Summary of main results

We included seven studies of treatments recommended by international clinical practice guidelines (CPGs) for the management of Type 2 diabetes. Objective tests of cognitive function were used in all seven studies, but two studies did not report useable data. Consequently, data were available for three comparisons: 1) repaglinide versus glibenclamide (glyburide) (one study); 2) standard versus intensive glycaemic control (three studies); and 3) rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin (one study).

1. Repaglinide versus glibenclamide (glyburide): we identified one study with 156 older people (age range 60 to 78 years) with Type 2 diabetes. Using this study in our analysis, we found low-quality evidence of a small advantage on global cognitive function measured with the MMSE for glibenclamide (glyburide) over repaglinide after 12 months of treatment. However, we identified no difference in a composite score of attention and executive functions. The difference in MMSE score was 0.9 points. No Minimal Clinically Important Difference (MCID) for prevention studies has been established, but in participants without cognitive impairment at baseline the MMSE has a 'ceiling effect' (Spencer 2013), and the FDA considers any statistically significant difference in cognitive outcomes in a prevention trial to be of interest (FDA 2013). Hence a difference of 0.9 MMSE points, although smaller than is often considered clinically important in dementia treatment trials, may be important in this context.

2. Intensive versus standard glycaemic control: we found four studies with 16,081 participants, but only two studies with 13,934 participants had extractable efficacy data and three studies with 14,908 participants had extractable data on adverse effects. We found moderate-quality evidence to suggest that there is probably little or no difference between intensive and standard treatment regimes on global cognitive function measured with the MMSE. We also found moderate-quality evidence of no effect on several cognitive subdomains. We found low-quality evidence from one study suggesting that there may be no difference in the incidence of dementia; moderate-quality evidence from two studies that patients receiving an intensive treatment strategy are more likely to experience at least one severe hypoglycaemic episode; and low-quality evidence from three studies that the treatment strategies may not be associated with any difference in all-cause mortality.

3. Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin: we found only one study with 145 participants. We found low-quality evidence to suggest that there may be little or

no difference in cognitive speed or working memory, but that there may be a small advantage for rosiglitazone plus metformin over glibenclamide (glyburide) plus metformin on episodic memory.

Overall completeness and applicability of evidence

The studies identified for inclusion in this review were insufficient to address all of its objectives.

We found data on only two comparisons of different drug regimes. Both were small and relatively short studies and both used glibenclamide (glyburide) in one study arm. This is a long-acting sulphonylurea associated with a high risk of hypoglycaemia and is contraindicated in those over 65 years old (AGS 2012; ADA 2017d). Therefore, we believe that these studies are not helpful to clinicians who are treating older people, in whom Type 2 diabetes is most common.

More data were available to compare intensive with standard glycaemic control. For this comparison we could include data from three much larger studies. One study focused on people older than 55 years with a high risk for cardiovascular disease events (Launer 2011). The intensive glycaemic control group in this study had a target HbA1c of less than 6.0% and the standard control group had a target HbA1c between 7.0% and 7.9%. Since this study was conducted, the target HbA1c in current clinical practice guidelines (CPGs) has been reduced to less than 6.5% (NICE 2016; AACE/ACE 2017) or less than 7% (ADA 2017e). The standard control group in the trial has the HbA1c now expected for people who are frail, disabled, or have multiple comorbidities, although trial participants did not have these characteristics (ADA 2017d). Therefore the findings in this trial might not be very applicable to current practice. The second study, ADVANCE 2008, focused on patients aged over 55 years at the start of the study (mean 66 years) and with a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease. The intensive glycaemic group was treated with gliclazide plus other treatments to achieve a HbA1c of 6.5% or less, while the standard group was treated on the basis of local guidelines. This intensive glycaemic control is similar to the goal of current CPGs (ADA 2017c; NICE 2016); hence the results of this study might be more useful to answer our clinical question, especially considering the long follow-up of five years. However, although the study evaluated global cognition and mortality, the incidence of dementia or MCI was not an outcome. The third study in this comparison, Zimring 2016, focused on participants from the Veteran Affairs Medical Centers in US who were older than 41 years and who were non-responsive to a maximum dose of at least one oral agent or daily insulin injections, or both. A limitation of this study in the context of our clinical question is the average age of only 60 years at the start of the study, so that the study population was at low risk of cognitive decline over the five-year follow-up period.

An important point to note is that our analyses are not adjusted for the level of glycaemic control such as HbA1c, fasting plasma glucose (FPG), or postprandial plasma glucose. Abbatecola 2006 did adjust some analyses for haemoglobin A1c and coefficient of variation of FPG and found that the statistically significant differences in the composite score and MMSE were maintained. Ryan 2006 found some correlation between FPG and reduction in Paired Associates Learning (PAL) errors for both treatments (Ryan 2006).

The included studies had a wide range of durations. Three of the seven studies had a follow-up for five years or more but only one of these had extractable data on cognition. Two studies had only six months of follow-up. A prolonged follow-up is necessary to detect those people who will progress to MCI or dementia over time, probably the most important cognitive outcomes in studies of this nature. The MMSE is not sensitive enough to detect small changes in cognition over short time periods and this is a limitation of those studies with short follow-up.

Overall, the review is limited by the small number of included studies and limited range of comparisons. Few studies of the efficacy of treatments for Type 2 diabetes have included measures of cognition. Where cognition has been studied, the tools used have not been standardised, and each study has used scales which evaluate different cognitive domains. This makes it very difficult to compare the findings of these studies.

Quality of the evidence

We evaluated the quality of evidence according to the GRADE approach (Guyatt 2008). This considers study limitations, directness of the evidence, heterogeneity in the data, precision of effect estimates, and other reasons to downgrade the quality (including indications of publication bias). In this review, we evaluated the overall quality of evidence for all results to be low or moderate, meaning that our confidence in the results is limited. Reasons for rating down the quality of evidence were risk of bias in the included studies and imprecision of the results or small sample sizes.

Potential biases in the review process

It is likely that we identified all relevant studies due to the strengths of the search strategy. We were, however, unable to obtain the data we needed from study authors when it had not been included in the published papers.

We have excluded some studies which report cognitive effects of treatments of Type 2 diabetes by deciding to exclude interventions that are not recommended by international CPGs (Sotaniemi 1995; Qiang 2015). However, we consider this exclusion to be important in order to represent usual clinical practice.

Agreements and disagreements with other studies or reviews

The question whether Type 2 diabetes treatments could have some positive effect over cognition or decrease the incidence of dementia in randomised clinical trials has, to our knowledge, been evaluated only by one other meta-analysis (Tuligenga 2015). Tuligenga's review focused on intensive glycaemic control versus standard glycaemic control and the search was up to date until October 2014 in MEDLINE and ALOIS. It included five studies, of which we included only two. The reason why we did not include the Cukierman-Yaffe 2014 study is because this study was not only focused on Type 2 diabetes but included participants with impaired glucose tolerance and impaired fasting glucose. Data for Type 2 diabetes patients were not reported separately. We also excluded Weinstock 2011 because the intervention — telemedicine — is not an approved intervention by international CPGs for Type 2 diabetes; and Koekkoek 2012, which did not assess cognition at baseline. Tuligenga 2015 also found no differences in cognitive function between the intensive glycaemic control group and the

standard glycaemic control group, in agreement with our results for this comparison.

AUTHORS' CONCLUSIONS

Implications for practice

From the evidence available, there is no reason to favour any particular type of diabetic treatment in order to prevent cognitive impairment in people with Type 2 diabetes.

Implications for research

This review shows that the question of the effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia studied in these trials should not be regarded as answered. Further research regarding the different treatments for Type 2 diabetes should include reliable and

validated measures of cognitive function. A battery of tests covering a range of domains of cognitive function is desirable, to detect differential changes and to assist in avoiding confounding from factors such as education and premorbid abilities. Studies should be designed to permit analysis of changes in cognitive function in relation to the mechanisms and metabolic effects of treatment, in particular insulin and glucose levels, and indices of glucose homeostasis. Relationships of cognitive function with mood and other aspects of functional status and quality of life also need further elucidation.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abbatecola 2006

Methods	<p>Study design: randomised controlled trial.</p> <p>Unit of allocation: by individuals.</p> <p>Start date: September 2001 (initial recruitment).</p> <p>End date: September 2004 (final recruitment).</p> <p>Duration of participation: 12 months.</p>
Participants	<p>Participants: 156 older people with Type 2 diabetes (age range 60 to 78 years) volunteered for the study. Participants were selected from a group of approximately 250 individuals with diagnosed Type 2 diabetes from university outpatient offices. Physicians were asked to refer older persons with Type 2 diabetes who had not previously undergone any antidiabetic drug treatment to their offices where further selection was performed.</p> <p>Population description: not reported.</p> <p>Setting: academic centre.</p> <p>Method of recruitment of participants: recruited from outpatient university clinics and referred to the study office.</p> <p>Total number randomised: 156.</p> <p>Baseline imbalances: no significant differences were found between study groups.</p> <p>Age: glibenclamide (glyburide) group = 74.3 (SD 2.3) years; repaglinide group = 74.5 (SD 2.5) years.</p> <p>Sex: glibenclamide (glyburide) group = 41 female/38 male; repaglinide group = 39 female/38 male.</p> <p>Race (white): not reported.</p> <p>BMI: glibenclamide (glyburide) group = 26.7 (SD 0.4); repaglinide group = 27.1 (SD 0.2).</p> <p>Glycated haemoglobin, standardised level-%</p> <p>Glibenclamide (glyburide) group = 7.2 (SD 0.7).</p> <p>Repaglinide group = 7.3 (SD 0.8).</p>
Interventions	<p>Types of intervention: glibenclamide (glyburide) initially started with 2.5 mg twice a day, given up to 30 minutes before daily meals.</p>

Abbatecola 2006 (Continued)

Types of comparison: repaglinide initially started with 1 mg twice a day, given up to 30 minutes before daily meals.

To achieve target glycaemic control, titration adjustments were made according to World Health Organization recommendations over an initial 3-week period prior to the beginning of study protocol, but no data regarding the increasing doses were found in the reference given by the author in the study about this point.

Outcomes	<p>Global cognitive function: MMSE.</p> <p>Composite outcome: 'Cognition Composite Score' (attention and executive function)</p> <p>TMT-A, TMT-B, TMT-B minus TMT-A (DIFF B-A), Wechsler Adult Intelligence Scale-Revised Digit Span: Backward Digit Span (DSP-Backward), Wechsler Adult Intelligence Scale-Revised Digit Span: Forward Digit Span (DSP-Forward), Verbal Fluency Test.</p>
Notes	<p>Sample size calculation: sample size calculation, performed with an $\alpha = 0.05$ and a $\beta = 0.80$, was found to be at least 110 subjects in order to prove a significant decline of 3% to 4% in the MMSE at the 12th month.</p> <p>Funding: funded by the Second University of Naples (fiscal year 2004).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comments: no methods for generating a random sequence have been described.
Allocation concealment (selection bias)	Unclear risk	Comments: no methods for allocation concealment have been described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comments: no methods for blinding the participants have been described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comments: no methods for blinding the participants and personnel have been described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: 1. "All MRI evaluations were made by physicians not involved in the study and blind toward the study design." 2. "All cognitive evaluations were made by physicians who were unaware of both study design and patient treatment allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In the Repaglinide group 65/77 patients and in Glibenclamide (glyburide) group 63/79 patients completed the study, the analyses were performed according to the intention-to-treat (ITT) principle."
Selective reporting (reporting bias)	Unclear risk	Comments: no protocol identified.
Other bias	Low risk	Comments: none identified.

ADVANCE 2008

Methods	<p>Study design: factorial randomised controlled trial</p> <p>Unit of allocation: by individuals.</p> <p>Start date: June 2001 (initial recruitment)</p> <p>End date: March 2003 (final recruitment)</p> <p>Duration of participation: median follow-up = 5 years.</p>
Participants	<p>Participants: diagnosis of Type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease.</p> <p>Population description: not reported.</p> <p>Setting: 215 collaborating centres in 20 countries from Asia, Australasia, Europe, and North America.</p> <p>Method of recruitment of participants: not reported.</p> <p>Total number randomised: 11,140.</p> <p>Baseline imbalances: not reported.</p> <p>Age: intervention group = 66 (SD 6); standard group = 66 (SD 6).</p> <p>Sex (female): intervention group = 42.6%; standard group = 42.3%.</p> <p>Race (white): not reported.</p> <p>BMI: intervention group = 28.0 (SD 5); standard group = 28.0 (SD 5).</p> <p>Glycated haemoglobin, standardised level-%</p> <p>Mean Intervention group: 7.48 (SD 1.65).</p> <p>Standard group: 7.48 (SD 1.63).</p>
Interventions	<p>Types of intervention: intensive glucose control were given gliclazide (modified release, 30 mg to 120 mg daily) and were required to discontinue any other sulfonylurea, plus other treatments decided by their physicians, to achieve a glycated haemoglobin value of 6.5% or less.</p> <p>Types of comparison: participants in the standard-control group who were using gliclazide (modified release) when they entered the study were required to substitute this drug with another sulfonylurea, if continued therapy was required with target glycated haemoglobin levels defined on the basis of local guidelines.</p>
Outcomes	<p>Types of outcome measures: cognitive decline (reduction in the Mini-Mental State Examination score by at least 3 points, as compared with the baseline score) and dementia (DSM-IV) (dichotomous).</p> <p>All cause of mortality and hypoglycaemic events.</p>
Notes	<p>Sample size calculation: not reported for the cognitive outcome.</p> <p>Funding: supported by grants from Servier (the major financial sponsor) and the National Health and Medical Research Council of Australia (211086 and 358395). Servier manufactures gliclazide (modified release) and the fixed combination of perindopril and indapamide</p>
Risk of bias	
Bias	<p>Authors' judgement</p> <p>Support for judgement</p>

ADVANCE 2008 (Continued)

Random sequence generation (selection bias)	Low risk	<p>Quote: "Central, computer-based randomisation was stratified according to several factors".</p> <p>Comments: randomisation performed by central and computer-based software is considered adequate.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "Central, computer-based randomisation was stratified according to several factors".</p> <p>Comments: the central, computer-based randomisation provided adequate allocation concealment.</p>
Blinding (performance bias and detection bias) All outcomes	Unclear risk	<p>Comments: no methods for blinding of participants and personnel have been identified.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Comments: no methods for blinding of participants and personnel have been identified.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "An independent End Point Adjudication Committee, unaware of the group assignments, reviewed source documentation for all suspected primary end points and deaths."</p> <p>Comments: an independent committee for analysing the interim analysis and the outcomes is considered adequate.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "In the intervention group 4828/5571 and in control group 4741/5569 patients were assessed at final visit." "All analyses were conducted according to the intention-to-treat principle".</p> <p>Comments: over 85% of the participants were assessed at final visit and the analysis performed was with the ITT principle and is considered adequate.</p>
Selective reporting (reporting bias)	Low risk	<p>Comments: protocol identified (NCT00145925), no differences found in the outcomes reported in the protocol and the articles.</p>
Other bias	Low risk	<p>Comments: none identified.</p>

Araki 2012

Methods	<p>Study design: randomised controlled trial.</p> <p>Unit of allocation: by individuals.</p> <p>Start date: March 2001 (initial recruitment).</p> <p>End date: February 2002 (final recruitment).</p> <p>Duration of participation: 6 years.</p>
Participants	<p>Participants: inclusion criteria included age 65 to 85 years, HbA1c $\geq 7.9\%$ or HbA1c $\geq 7.4\%$ with at least one of following criteria: BMI ≥ 25 kg/m², blood pressure $\geq 130/85$ mmHg, serum total cholesterol ≥ 200 mg/dL (or low-density lipoprotein cholesterol (LDL-C) ≥ 120 mg/dL in participants without coronary heart disease (CHD)) or ≥ 180 mg/dL (or LDL-C ≥ 100 mg/dL in participants with CHD), triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL.</p> <p>Population description: diabetic outpatients.</p>

Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia (Review)

Araki 2012 (Continued)

Setting: outpatients at 39 Japanese hospitals.

Method of recruitment of participants: recruited from hospitals.

Total number randomised: 585 participants to the intervention group and 588 in the control group.

Baseline imbalances: significant baseline imbalances found in α -Blockers, EPA, and HbA1c.

Age: intervention group = 71.9 (SD 4.6); control group = 71.7 (SD 7.7).

Sex (female): intervention group = 53.7%; control group = 53.7%.

Race: not reported.

BMI: intervention group = 24.0 (SD 3.9); repaglinide group = 24.3 (SD 7.3).

Glycated haemoglobin, standardised level-%: intervention group = 8.5 (SD 0.9); control group = 8.4 (0.8).

Interventions	Types of intervention: the treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m2, systolic blood pressure (SBP) < 130 mmHg, diastolic blood pressure (DBP) < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if participants had CHD) or < 200 mg/dL (or LDL-C < 120 mg/dL if participants did not have CHD; Table 1). If HbA1c levels did not reduce to < 6.9%, oral hypoglycaemic drugs (sulphonylurea, biguanides, α-glucosidase inhibitors and pioglitazone) or insulin therapy was introduced by the physician. If total cholesterol or LDL-C levels did not reach the treatment goal, the physicians were advised to use atorvastatin. Participants with a history of cerebral infarction also had antiplatelet therapy where possible.	
	Types of comparison: the conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidaemia without a specific treatment goal. Each participant had a standardised medical history and physical examination at baseline, and then annually.	
Outcomes	Primary cognitive outcome: cognitive function measured by MMSE.	
	Secondary outcome: no secondary outcomes.	
Notes	Sample size calculation: not reported.	
	Funding: not reported.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 1173 diabetic outpatients were enrolled and randomly allocated to either the intensive or conventional treatment group. The randomised factors were age, sex, diabetes treatment, HbA1c, total cholesterol, triglycerides, HDL-C, blood pressure, diabetic microangiopathy, atherosclerotic disease, hypertension, hyperlipidaemia and institutions." Comments: no methodology for generating the random sequence has been reported.
Allocation concealment (selection bias)	Unclear risk	Comments: no methodology for allocation concealment has been reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comments: no methods regarding blinding of participants have been provided.

Araki 2012 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comments: no methods regarding blinding of personnel have been provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Possible clinical end-points were noted in the annual data sheets, with the diagnostic criteria for each endpoint being predetermined. When an end point was notified on a data sheet, the administrator requested full information from the data management and statistical analysis centre, followed by a review by two clinical assessors of the event assignment committee." Comments: despite the aforementioned information, they were not explicit about the existence of a blinding methodology of the assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All major analyses were according to assigned allocations (intention to treat), without exclusion of protocol deviants."
Selective reporting (reporting bias)	Low risk	Comments: UMIN000000890 protocol was identified
Other bias	Low risk	Comments: none identified.

Guo 2014

Methods	Study design: randomised controlled trial. Unit of allocation: by individuals. Start date: April 2013 (initial recruitment). End date: May 2013 (final recruitment). Duration of participation: 24 weeks.
Participants	Participants: participants with depression diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) and a Type 2 diabetes newly diagnosed by laboratory. Population description: not reported. Setting: not reported. Method of recruitment of participants: not reported. Total number randomised: 72 for both groups. Baseline imbalances: not reported. Age: intervention group = 54.7 (SD 7.3); control group = 53.3 (SD 7.3). Sex (male/female): intervention group = 17/12; control group = 19/10. Race (white): not reported. BMI: not reported. Glycated haemoglobin, standardised level-%: intervention group = 7.82 (SD 0.82); control group = 8.01 (SD 0.59).

Guo 2014 (Continued)

Interventions	<p>Types of intervention: metformin: the recommended starting dose for metformin is 0.5 g per tablet, two tablets per day with meals. If the blood glucose level is not well controlled after taking metformin for 7 days, the dose should be increased gradually to 1.5 g/day over a period of 2 weeks and the maximum dose should not exceed 2.0 g/day before each meal (three times per day) or before sleep.</p> <p>Types of comparison: placebo was vitamin C with the same appearance as the metformin tablet.</p>
Outcomes	<p>Primary cognitive outcome: no primary outcome reported. However, all outcomes are cognitive function measured by WMS-R subtest, verbal memory index, visual memory index, general memory index, attention and concentration, and delayed memory index.</p>
Notes	<p>Sample size calculation: not reported.</p> <p>Funding: this study was supported, in part, by a grant for diabetes research from Peking University, Program for Scientific Research Innovation Team in Colleges and Universities of Shandong Province and Taishan Scholars Construction Engineering.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "The present study was a randomised double-blind placebo-controlled study. The participants were randomly divided into either the metformin- or placebo-treated groups using random numbers."</p> <p>Comments: the participants were randomly divided into either the metformin- or placebo-treated groups using random numbers.</p>
Allocation concealment (selection bias)	Unclear risk	Comments: no methods for allocation concealment have been described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comments: no methods for blinding participants have been described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comments: no methods for blinding personnel have been described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comments: no methods for blinding outcome assessors have been described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comments: the initial number of participants were 72 and before the first five weeks 14 (19.4%) dropped out; the analyses were not performed according to the intention-to-treat (ITT) principle.
Selective reporting (reporting bias)	High risk	Comments: no protocol was identified; in the methods the follow up was until 24 weeks and the results showed in the study are only reported at 12 weeks.
Other bias	Low risk	Comments: none identified.

Launer 2011

Methods	Study design: double 2 × 2 factorial parallel group randomised trial.
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Launer 2011 (Continued)

Unit of allocation: by individuals.

Start date: August 2003 (initial recruitment).

End date: December 2005 (final recruitment).

Duration of participation: 40 months.

Participants

Participants: participants targeted by ACCORD MIND, which was done in 77 clinics in North America, were aged 45 to 79 years and had Type 2 diabetes, high HbA1c concentrations ($> 7.5\%$, > 58 mmol/mol), and a high risk for cardiovascular disease events suggested by significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease.

Population description: not reported.

Setting: the MIND participants were therefore drawn from 52 North American clinics in six of the seven clinical centre networks and participants younger than 55 years old were excluded.

Method of recruitment of participants: recruited from outpatient clinics.

Total number randomised: 1469 participants to the intervention group and 1508 in the control group (2794 analysed).

Baseline imbalances: not reported.

Age: intervention group = 62.3 (SD 5.7); control group = 62.7 (SD 5.9).

Sex (female): intervention group = 48%; control group = 49%.

Race (white): intervention group = 69.4%; control group = 69.9%.

BMI: intervention group = 33.0 (SD 5.4); control group = 32.9 (SD 5.3).

Glycated haemoglobin, standardised level-%

Intervention group: 8.3 (1.0).

Control group: 8.3 (1.1).

Interventions

Types of intervention: intensive glycaemic control;

(glycaemic treatment targeting HbA1c less than 6.0%, diabetes education, glucose-monitoring equipment, and antidiabetic medications to achieve this goal).

Therapy was intensified whenever HbA1c was $\geq 6\%$, or $> 50\%$ of capillary glucose readings were > 5.6 mmol/L (100 mg/dL). All drug combinations from a standard formulary were permitted; specific drugs were reduced only for side effects or contraindications).

Types of comparison: standard glycaemic control;

(glycaemic treatment targeting HbA1c to 7.0% to 7.9%, diabetes education, glucose-monitoring equipment, and antidiabetic medications to achieved this goal).

Therapy was intensified whenever HbA1c was $\geq 8\%$, or $> 50\%$ of capillary glucose readings were > 7.8 mmol/L (140 mg/dL). Antihyperglycemic drugs that promoted hypoglycaemia (i.e. insulin or insulin secretagogues) were reduced if HbA1c was persistently lowered to $< 7\%$. All drug combinations from a standard formulary were permitted; specific drugs were reduced only for side effects or contraindications).

Outcomes

Types of outcome measures

Primary cognitive outcome:

- Digit Symbol Substitution Test.

Launer 2011 (Continued)

Secondary outcome:

- Total brain volume (MRI).
- Memory (Rey Auditory Verbal Learning Test (RAVLT)).
- Executive function (Stroop test).
- General cognitive function (MMSE).
- All-cause mortality.
- Hypoglycaemic events.

Notes

Sample size calculation: for the planned comparison of cognitive function between the intensive glycaemic control and standard glycaemic control groups, using a 2-sided significance level of 0.05, a sample of 1400 per group provides approximately 90% power to detect a difference of 1.0 between 40-month mean DSST scores. For the comparison of cognitive function between the intensive blood pressure control and standard blood pressure control groups (or fibrate versus placebo in the lipid trial), using a 2-sided significance level of 0.05, this sample size will provide approximately 80% power to detect a difference of 1.2 on the 40-month mean DSST scores. To account for a 15% loss to follow-up, the recruitment of 350 participants was planned within each cell.

Funding: funded by US National Institute on Aging and US National Heart, Lung, and Blood Institute.

Arm cancelled: the intensive intervention was stopped on 6 February 2008, when an increased risk (hazard ratio 1.22, 95% CI 1.01 to 1.46) for mortality was reported; participants in that group were moved to standard glycaemic treatment. MIND assessments continued in accordance with the original protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "The CCC computer generated unique randomisation sequences for every clinical site and electronically verified exclusion and inclusion criteria for every individual before assigning a treatment group. Clinic staff implemented the randomisation via secure access to the ACCORD trial website".</p> <p>Comments: computer generated unique randomisation sequences were considered adequate.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "The CCC computer generated unique randomisation sequences for every clinical site and electronically verified exclusion and inclusion criteria for every individual before assigning a treatment group. Clinic staff implemented the randomisation via secure access to the ACCORD trial website."</p> <p>Comments: allocation concealment was considered adequate.</p>
Blinding (performance bias and detection bias) All outcomes	High risk	<p>Quote: "Glycaemia trial treatment assignment was open label, and both clinic staff and patients were aware of the assigned glycaemic goal."</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "Glycaemia trial treatment assignment was open label, and both clinic staff and patients were aware of the assigned glycaemic goal."</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Comments: it is unclear whether the outcome assessors were blinded in the interim and final analyses.</p>

Launer 2011 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comments: approximately 10% of the participants were lost to follow-up and no reasons have been given. No information has been given about the statistical analyses used to correct for missing values.
Selective reporting (reporting bias)	Low risk	Comments: protocol identified (NCT00182910), no differences found in the outcomes reported in the protocol and the articles.
Other bias	Low risk	Comments: none identified.

Ryan 2006

Methods	<p>Study design: randomised controlled trial</p> <p>Unit of allocation: by individuals.</p> <p>Start date: not reported.</p> <p>End date: not reported.</p> <p>Duration of participation: 24 weeks.</p>
Participants	<p>Participants: 145 adults with Type 2 diabetes were recruited from 18 centres in the US. Adults were eligible if they were receiving oral metformin combination therapy and had HbA1c (A1C) $\leq$ 8%, BMI $\leq$ 27 kg/m², no evidence of dementia (score $\geq$ 27 on the Mini-Mental State Examination), and no evidence of current depression as determined by the Mini International Neuropsychiatric Interview (MINI).</p> <p>Population description: not reported.</p> <p>Setting: not reported.</p> <p>Method of recruitment of participants: not reported.</p> <p>Total number randomised: 145.</p> <p>Baseline imbalances: imbalances found on fasting insulin (pmol/l) and C-peptide (nmol/l).</p> <p>Age: rosiglitazone plus metformin group = 60.7 (SD 1.0 years); glibenclamide (glyburide) plus metformin group = 59.6 (SD 0.8 years).</p> <p>Sex (female): rosiglitazone plus metformin group = 43%; glibenclamide (glyburide) plus metformin group = 36% female.</p> <p>Race (Caucasian): rosiglitazone plus metformin group = 80%; glibenclamide (glyburide) plus metformin group = 79%.</p> <p>BMI: rosiglitazone plus metformin group = 33.8 (SD 0.7); glibenclamide plus metformin group = 32.5 (SD 0.06).</p> <p>Glycated haemoglobin, standardised level-%</p> <p>Rosiglitazone plus metformin group: 7.6 (SD 0.1).</p> <p>Glibenclamide (glyburide) plus metformin group: 7.6 (SD 0.1).</p>
Interventions	<p>Types of intervention: rosiglitazone plus metformin group.</p> <p>During the first 8 weeks of treatment, study medication was given as 4.0 mg rosiglitazone once daily. To titrate participants to equal glycaemic control, FPG was assessed at weeks 8 and 16, and the dose was adjusted if FPG $\geq$ 7.8 mmol/l. Rosiglitazone could be increased to 8 mg once daily or 4 mg twice daily.</p> <p>No changes were made to the background dose of metformin during blinded treatment.</p>

Ryan 2006 (Continued)

Types of comparison: glibenclamide (glyburide) plus metformin group

During the first 8 weeks of treatment, study medication was given as 2.5 mg twice daily, with glibenclamide (glyburide) increased to 2.5 mg twice daily after 4 weeks of treatment. To titrate participants to equal glycaemic control, FPG was assessed at 8 and 16 weeks, and the dose was adjusted if FPG > 7.8 mmol/l. Glibenclamide (glyburide) could be increased to 5 mg twice daily or up to a maximal dose of 7.5 mg twice daily.

No changes were made to the background dose of metformin during blinded treatment.

Outcomes	Types of outcome: <ul style="list-style-type: none">• Digit Symbol Substitution Test• Rey Auditory Verbal Learning Test (immediate)• Cambridge Neuropsychological Test Automated Battery (CANTAB)<ul style="list-style-type: none">• Paired Associates Learning (PAL)• Pattern Recognition Memory• Spatial Working Memory Test• Rapid Visual Information Processing• Reaction Time As composite outcome (cognitive domains): <ul style="list-style-type: none">• Working memory (sum of z-scores of CANTAB PAL, CANTAB Rapid Visual Information Processing, CANTAB Spatial Working Memory Test and Digit Symbol Substitution Test)• Learning Ability (sum of z-scores of Rey Total Learning Score, Pattern Recognition Memory)• Cognitive Efficiency (sum of z-scores of Rey Forgetting Score and Reaction time)	
Notes	Sample size calculation: not reported for the cognitive outcome. Funding: not reported.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For random assignment to treatment, we used a computer-generated allocation sequence." Comments: computer-generated allocation sequence is considered adequate.
Allocation concealment (selection bias)	Unclear risk	Comments: no methods for allocation concealment have been identified.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comments: no methods for blinding of participants and personnel have been identified.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comments: no methods for blinding of participants and personnel have been identified.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Cognitive tests were administered at week 0 and again at week 24 by staff blinded to subjects' treatment assignment." Comments: outcome assessors seemed to be blinded.

Ryan 2006 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The intent-to-treat population consisted of all randomised subjects with at least one valid observation for an efficacy variable while receiving treatment." In table 2, the in cognitive scores were in rosiglitazone plus metformin group 66/69 and in glibenclamide (glyburide) plus metformin group was 70/72 Comment: ITT analysis is considered adequate.
Selective reporting (reporting bias)	Unclear risk	Comments: no protocol identified.
Other bias	Low risk	Comments: none identified.

Zimering 2016

Methods	<p>Study design: randomised controlled trial.</p> <p>Unit of allocation: by individuals.</p> <p>Start date: December 2000 (initial recruitment).</p> <p>End date: May 2003 (final recruitment).</p> <p>Duration of participation: 5 years.</p>
Participants	<p>Participants:</p> <p>The participants were recruited from 20 participating Veteran Affairs Medical Centers in the USA.</p> <p>Inclusion criteria included > 41 years old, who are non-responsive to a maximum dose of at least one oral agent and/or daily insulin injections. Non-responsiveness is defined as having centrally measured HbA1c level > 4 standard deviations above the normal mean, that is, > 7.5%, or else local HbA1c > 8.3%.</p> <p>Population description: not reported</p> <p>Setting: people from 20 participating Veteran Affairs Medical Centers in the USA, no additional data regarding the setting was described.</p> <p>Method of recruitment of participants: not reported</p> <p>Total number randomised: 892 participants to the intensive group and 899 in the standard group.</p> <p>Baseline imbalances: no significant baseline imbalances were found.</p> <p>Age: intensive group = 60.5 (SD 9.0); standard group = 60.3 (SD 9.0).</p> <p>Sex (female): intensive group = 53.7%; standard group = 53.7%.</p> <p>Race: in the intensive group there were 539 non-Hispanic white, 155 Hispanic white, 152 black and 46 participants with other race. In the standard group there were 572 non-Hispanic white, 136 Hispanic with, 147 black and 44 participants with other race.</p> <p>BMI: intensive group = 31.3 (SD 3.0); standard group = 31.2 (SD 4.0).</p> <p>Glycated haemoglobin, standardised level-%: intensive group = 9.4 (SD 2.0); standard group = 9.4 (SD 2.0).</p>
Interventions	<p>In both study groups, participants with a BMI of 27 or more were started on two oral agents, rosiglitazone plus metformin; those with a BMI of less than 27 were started on rosiglitazone plus glimepiride.</p>

Zimering 2016 (Continued)

Types of intervention: participants in the intensive-therapy group were started on maximal doses. Before any change in oral medications, insulin was added for those who did not achieve a glycated haemoglobin level of less than 6%. Subsequent changes in medication were determined according to protocol guidelines and local assessment. The guidelines allowed for the use of any approved drug at the discretion of the investigator. The goal for glycated haemoglobin levels was an absolute reduction of 1.5 percentage points.

Types of comparison: participants in the standard-therapy group were started on half the maximal doses. Before any change in oral medications, insulin was added for those who did not achieve a glycated haemoglobin level of less than 9%. Subsequent changes in medication were determined according to protocol guidelines and local assessment. The guidelines allowed for the use of any approved drug at the discretion of the investigator.

Other modifiable cardiovascular risk factors were treated identically in the two study groups. Treatment guidelines (based on recommendations of the American Diabetes Association, which were updated as necessary) for blood pressure and lipid control, as well as for dietary, exercise, and diabetes education, were provided to all participants.

All participants were prescribed aspirin and a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) unless contraindicated.

Outcomes	Types of outcome measures: TMT-B. Digit Span. Digit symbol substitution task (DSym). All cause of mortality. Hypoglycaemic events.
Notes	There is a difference of 3 participants in standard group between the original study (Duckworth 2009) and Zimering 2016 . Data from mortality and hypoglycaemia were reported in Duckworth 2009 .

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients without significant renal insufficiency or congestive heart failure were randomly assigned to STD vs. INT glycaemic treatment". Comments: no methodology for generating a random sequence has been reported.
Allocation concealment (selection bias)	Unclear risk	Comments: no methodology for allocation concealment has been reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comments: no methodology for blinding participants, personnel, or outcome assessors has been reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comments: no methodology for blinding participants, personnel, or outcome assessors has been reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Comments: no methodology for blinding participants, personnel, or outcome assessors has been reported.

Zimering 2016 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comments: statistical analyses to account for participants that were lost to follow-up are not specified and it is not clear how many participants were lost before final analysis.
Selective reporting (reporting bias)	Low risk	Comments: protocol identified (Abraira 2003); no differences found in the outcomes reported in the protocol and the articles.
Other bias	Unclear risk	Comments: none identified.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baker 2010	Wrong participants: prediabetes participants.
Cukierman-Yaffe 2014	Wrong participants: dysglycemia participants.
Daly 2014	Wrong intervention: it compared ingestion of a whey-protein drink combined with vitamin D supplementation.
Davies 2015	Wrong intervention: group self-management plus personalised genetic- and lifestyle-associated risk information.
Espeland 2016	Wrong design: no cognitive evaluation at baseline.
Gatskikh 2015	Wrong intervention: intervention group received a complex metabolic drug cytoflavin daily intravenously.
Gilchrist 2014	Wrong intervention: nitrate-depleted beetroot juice is not an accepted treatment for Type 2 diabetes.
Gradman 1993	Wrong design: non-randomised and inappropriately controlled trial.
Inouye 2015	Wrong intervention: it compared cognitive behavioural therapy to diabetes education and support.
Luchsinger 2011	Wrong intervention: telemedicine is not an accepted treatment for Type 2 diabetes.
Meneilly 1993	Wrong design: no control group.
Naor 1997	Wrong setting: inpatient treatment.
NCT02415556	Wrong intervention: 40 IU of intranasal insulin (INI) compared to placebo (sterile saline).
NCT02486341	Wrong outcome: intra-day glycaemic variability according basal insulin at 5 days.
NCT02879409	Wrong outcome: determination of the variability of HbA1c.
Padwal 2016	Wrong intervention: home BP telemonitoring, used with or without protocolised case management, compared with “enhanced usual care”.

Study	Reason for exclusion
Qiang 2015	Wrong intervention: interventional proposed treatment is the Sancaijiangtang powders (with pioglitazone hydrochloride) used in traditional medicine, which is not an accepted treatment for Type 2 diabetes in international guidelines.
Sotaniemi 1995	Wrong intervention: this study was focused on the effect of ginseng which is not an accepted treatment for Type 2 diabetes.
Testa 1998	Wrong outcome: subjective impressions of cognitive function.
Tovi 1998	Wrong outcome: subjective impressions of cognitive function.
UKPDS 1999	Wrong outcome: subjective impressions of cognitive function.
Vijayakumar 2011	Wrong intervention: Vitamin E is not approved by international guidelines for Type 2 diabetes.
Wong 2016	Wrong intervention: resveratrol consumption is not approved by international guidelines for Type 2 diabetes.

Characteristics of ongoing studies *[ordered by study ID]*

[ACTRN12614000222640](#)

Trial name or title	Cognition and Type 2 Diabetes – A pilot randomised controlled trial (RCT) of exercise
Methods	Interventional study. Randomized controlled trial.
Participants	50 participants between 50 and 75 years old will be recruited. Inclusion criteria: 1) Type 2 diabetes as diagnosed by fasting blood glucose greater or equal to 7 mmol/L or HbA1C greater than 6.4% or 2-hr post-prandial glucose greater than 11 mmol/L according to current American Diabetes Association Guidelines; 2) age 50 to 75 years; 3) be willing and able to participate in a structured exercise program for 6 months. Exclusion criteria: 1) any severe medical condition that precludes safe participation in exercise; 2) moderate or severe dementia; 3) known central nervous system disorders that may have confounding effects on cognitive function (e.g. tumour, multiple sclerosis, Parkinson's disease); 4) contra-indication to MRI; 5) exercising greater than the equivalent of 30 minutes once a week in the last 3 months.
Interventions	The intervention group will receive a 6-month structured exercise program by fully trained exercise physiologists. Two one-hour supervised sessions per week will occur at the Menzies Research Institute gymnasium on non-consecutive days, plus a further one-hour per week unsupervised session at the participant's home with prescribed exercises (e.g. walking). Each supervised session will consist of a warm-up and cool-down, moderate- to high-intensity progressive resistance training exercises using body weight, simple machine or free weights of 8 to 15 repetitions (e.g. free weights: bicep curls, shoulder press, chest press; body weight: step ups or sit to stand ± weight vest; machine weights: quadriceps press, shoulder press, chest press, knee extension), and an aerobic component involving stationary cycling, cross-trainer or treadmill walking at 40% to 84% of VO ₂ R. The program will be tailored to participant's abilities and progressive intensity applied with increasing fitness. Adherence will be assessed by attendance at the supervised exercise sessions and completion of personal exercise diaries.
Outcomes	Assessments of selective attention, executive function, processing speed and memory will be made using standard neurological tests: Hopkins Verbal Learning Test – R, Form 1; Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Subsets of Digit Span, Digit Symbol Coding and Symbol Search; Controlled Oral Word Associ-

ACTRN12614000222640 (Continued)

ation Test (COWAT); Category Fluency Test; Rey Complex Figure copying and delayed recall task; Stroop Test (Victoria Form); Trails A & B.

Starting date	28 March 2014
Contact information	Name: Dr Michele Callisaya. Stroke and Ageing Research Group Southern Clinical School Level 5 E Block, Monash Medical Centre Monash University 246 Clayton Road, Clayton, Victoria 3168, Australia Telephone: +61 3 62264785 Email: michele.callisaya@monash.edu
Notes	Study status: recruiting participants.

NCT02348801

Trial name or title	Lifestyle Intervention for Senior Diabetics (LISD)
Methods	Interventional study. Randomized, parallel assignment, open label treatment study
Participants	<p>Subjects will be older (age 65 to 85 years) adults with Type 2 diabetes. Diabetes will be determined by self-report with verification (medical records, current treatment, confirmation from health care provider, fasting glucose ≥ 126 mg/dL, symptoms of hyperglycaemia with plasma glucose ≥ 200 mg/dL or 2-hour plasma glucose ≥ 200 mg/dL after a 75 g glucose load on at least two occasions, or HbA1C of $\geq 6.5\%$). All subjects will have a BMI of ≥ 27 kg/m² and have stable weight (± 2 kg) and on stable medications during the last 6 months.</p> <p>Volunteers will be excluded if they fail to provide informed consent, have any major comorbid disease that is uncontrolled, or any condition that is likely to limit life span and/or affect the safety of the interventions, or interfere with the conduct of the trial.</p>
Interventions	<p>Intervention group: the participants will receive therapy sessions designed to acquire positive weight-control skills and attitudes, and practice weight-maintenance skills. A balanced diet will be prescribed to provide a deficit of 500 to 750 kcal/day from daily energy requirement and exercise sessions of ~ 90 min duration (15 min warm-up of flexibility exercise, followed by ~ 30 min of aerobic exercise; after a brief rest period, ~ 30 min of resistance training; and finally ~ 15 min balance exercise) conducted three times weekly supervised at [an] exercise facility for first six months, and regular exercises continued at community-fitness centres and at home for the following six months.</p> <p>Control group: diabetes support and education.</p>
Outcomes	<p>Change in the modified mini-mental state exam at 12 months.</p> <p>Change in Stroop colour naming test at 12 months.</p> <p>Change in word list fluency test at 12 months.</p> <p>Change in Ray auditory verbal learning test (RAVLT) at 12 months.</p> <p>Change in Trail A/B at 12 months.</p> <p>Change in composite cognitive z-score at 12 months.</p>
Starting date	January 2015
Contact information	<p>Dennis T Villareal 713-794-7156 email: dennis.villareal@bcm.edu</p> <p>Alessandra Celli 713-578-4300 email: Alessandra.celli@va.gov</p>
Notes	Study status: recruiting participants.

NCT02409238

Trial name or title	Insulin Resistance and Mild Cognitive Impairment (MCI) in Older Chinese Adults With Pre-Diabetes and Diabetes: Cognitive Effects of Lifestyle Intervention and Metformin Treatment in a Randomized Controlled Trial
Methods	Interventional study. Randomized controlled trial.
Participants	<p>360 participants, 55 years old and older.</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1) Chinese Singapore Citizen or permanent resident. 2) BMI of 23 or higher; and/or waist circumference ≥ 90 cm and ≥ 80 cm for Chinese men and women respectively. 3) Prediabetes (if not diabetic). 4) Type 2 diabetes (if not prediabetic) yet to be treated with anti-diabetic drug treatment ('on diet control only'), with HbA1c $< 8.0\%$ OR diabetics who have been taken off medication for ≥ 1 year with HbA1c $< 8.0\%$ will be considered for recruitment. 5) Mild cognitive impairment. <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1) Contraindications to metformin treatment: creatinine of > 150 $\mu\text{mol/L}$, history of decompensated liver disease, liver cirrhosis, or unexplained elevated hepatic transaminases (ALT or AST $> 3\times$ upper limit of normal (upper limits as accepted by SingHealth Polyclinics as 66 U/L for ALT and 42 U/L). This contraindication would not affect subjects with a history of high baseline ALT and/or AST which have been evaluated by a hepatologist to be due to non-alcoholic fatty liver disease without cirrhosis. 2) Severe neuro-musculoskeletal and sensory disabilities. 3) Severe psychiatric disorders (e.g. alcohol abuse, severe depression, schizophrenia, bipolar disorder). 4) illnesses that seriously reduce life expectancy or ability to participate in the trial. 5) Congestive heart failure (New York Heart Association cardiac status classes 2, 3 or 4), myocardial infarction or coronary artery bypass surgery or percutaneous coronary intervention within the past 6 months, cardiac arrhythmias, severe hypertension. 6) Concurrent use or recent use (within 1 week or 5 half-lives of the drug whichever is longer) of drugs with anticholinesterase, sedating or central nervous system (CNS) side effects: antispasmodics, antiemetics, antidiarrhoeal, antihistamines, hypnotics, antidepressants, antipsychotics, bronchodilators. 7) Concurrent use of drugs (for > 4 consecutive weeks) or use of drugs within 12 weeks of screening that are known to adversely affect glucose tolerance and its interpretation. 8) History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. 9) Use of an investigative drug within 30 days or 5 half-lives of the drug whichever is longer. 10) Potentially unreliable and/or judged by the investigator to be unsuitable for the study.
Interventions	This 3-year open-label study aims to recruit 360 subjects with 50% (180 subjects) randomised to receiving intensive lifestyle intervention with metformin (if diabetic) vs the other 50% who would receive only the usual standard level of care in the primary care setting.
Outcomes	Change in composite z-score of memory and multi-domain non-amnesic cognitive test performance using a neuropsychological assessment performed at baseline and at 2 years.

NCT02409238 (Continued)

Change in subjective memory and cognitive complaint (SMCC) as measured at baseline and at 2 years.

Change in Cognitive Instrumental Activities of Daily Living Scale (Cog-IADL) as measured at baseline and at 2 years.

Change in Global Clinical Dementia Rating Sum of Boxes (version with Informant and version without need for Informant – CDR-SB) as measured at baseline and at 2 years.

Change in Mini-Mental State Examination (MMSE) as measured at baseline and at 2 years.

Change in Montreal Cognitive Assessment scale (MoCA) as measured at baseline and at 2 years.

Starting date	April 2015
Contact information	Name: Wee Kien Han, Andrew; MCI Address: SingHealth Polyclinics - Marine Parade Polyclinic Singapore, Singapore, 440080; Telephone: 65-96615423; email: andrew.wee@singhealth.com.sg
Notes	Study status: recruiting participants.

Watson 2015

Trial name or title	A randomised trial comparing low-fat diets differing in carbohydrate and protein ratio, combined with regular moderate intensity exercise, on glycaemic control, cardiometabolic risk factors, food cravings, cognitive function and psychological well being in adults with type 2 diabetes
Methods	Interventional study. Randomized controlled trial
Participants	<p>61 participants, 18 to 70 years old</p> <p>Inclusion criteria: diagnosed with Type 2 diabetes, aged 18 to 70 years, HbA1c between 6.5% and 10.5% at screening, BMI greater than 25 kg/m², weight ≤ 135 kg (maximum capacity for dual X-ray absorptiometry (DEXA)), non-smoker for more than 6 months, proficient in written and spoken English (to perform the cognitive tests), age-appropriate cognitive abilities (determined using the Dem-Tect questionnaire).</p> <p>Exclusion criteria: liver, kidney, gastrointestinal or cardiovascular disease, respiratory disease (apart from stable asthma), retinopathy, malignancy (within last 6 months), proteinuria, uncontrolled hypertension (N170/100), taking medication for a neurological or psychiatric condition (except stable antidepressants N3 months), neurological or psychiatric condition, history of head or brain injury, musculoskeletal injury or peripheral vascular disease sufficient to impede exercise, undertaking a weight loss programme or taking appetite suppressants, pregnant or lactating, unable to participate in the trial for 6 months if participated in another study within last 30 days.</p>
Interventions	Overweight/obese adults with Type 2 diabetes were randomised to consume either a HP diet (n = 32, ~ 32% protein, 33% carbohydrate, 30% fat) or a higher-carbohydrate diet (HC, n = 29, ~ 22% protein, 51% carbohydrate, 22% fat) for 24 weeks with 30 min of moderate intensity exercise five days/week for the study duration. There were 2 phases: a 12-week weight loss phase; followed by a 12-week weight maintenance phase.
Outcomes	<p>Memory.</p> <p>Psychomotor and executive function.</p> <p>Outcomes will be measured at baseline and the end of each 12-week intervention phase.</p>
Starting date	Not available.

Watson 2015 (Continued)

Contact information

Name: Watson NA. Address: Alliance for Research in Exercise, Nutrition and Activity, Sansom Institute for Health Research, University of South Australia, GPO Box 2471, Adelaide, SA 5001, Australia; email: nerylee.watson@mymail.unisa.edu.au

Notes

DATA AND ANALYSES
Comparison 1. Glibenclamide (glyburide) versus repaglinide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MMSE at 12 months	1	156	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.68, -0.12]
2 Cognition composite score at 12 months	1	156	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.01, 0.01]

Analysis 1.1. Comparison 1 Glibenclamide (glyburide) versus repaglinide, Outcome 1 MMSE at 12 months.

Study or subgroup	Glibenclamide		Repaglinide		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Abbatecola 2006	79	24.1 (2.5)	77	25 (2.5)		100%	-0.9[-1.68,-0.12]
Total ***	79		77			100%	-0.9[-1.68,-0.12]
Heterogeneity: Not applicable							
Test for overall effect: Z=2.25(P=0.02)							
					Glibenclamide		Repaglinide

Analysis 1.2. Comparison 1 Glibenclamide (glyburide) versus repaglinide, Outcome 2 Cognition composite score at 12 months.

Study or subgroup	Glibenclamide		Repaglinide		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Abbatecola 2006	79	0 (0)	77	0 (0)		100%	-0[-0.01,0.01]
Total ***	79		77			100%	-0[-0.01,0.01]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.24(P=0.81)							
					Glibenclamide		Repaglinide

Comparison 2. Intense glycaemic control versus standard glycaemic control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global cognitive function measured by MMSE 40 months	1	2794	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.08, 0.07]
2 Global cognitive function (defined as reduction of at least 3 points in the MMSE)	1	11140	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.08]
3 Executive function measured by Stroop test at 40 months	1	2794	Mean Difference (IV, Random, 95% CI)	-0.61 [-1.62, 0.40]
4 Episodic memory measured by RAVLT at 40 months	1	2794	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.14, 0.12]
5 Speed measured by DDST at 40 months	1	2794	Mean Difference (IV, Random, 95% CI)	0.32 [-0.28, 0.92]
6 Incidence of dementia (defined as dementia according to DSM-IV)	1	11140	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.87, 1.85]
7 Hypoglycaemia	2	12931	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.52, 3.14]
8 All cause mortality	3	15888	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.13]

Analysis 2.1. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 1 Global cognitive function measured by MMSE 40 months.

Analysis 2.2. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 2 Global cognitive function (defined as reduction of at least 3 points in the MMSE).

Analysis 2.3. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 3 Executive function measured by Stroop test at 40 months.

Analysis 2.4. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 4 Episodic memory measured by RAVLT at 40 months.

Analysis 2.5. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 5 Speed measured by DDST at 40 months.

Analysis 2.6. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 6 Incidence of dementia (defined as dementia according to DSM-IV).

Analysis 2.7. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 7 Hypoglycaemia.

Analysis 2.8. Comparison 2 Intense glycaemic control versus standard glycaemic control, Outcome 8 All cause mortality.

Comparison 3. Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite outcome: working memory	1	136	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.69, 0.49]
2 Composite outcome: learning ability	1	136	Mean Difference (IV, Random, 95% CI)	0.0 [-0.54, 0.54]
3 Composite outcome: cognitive efficiency	1	136	Mean Difference (IV, Random, 95% CI)	-0.1 [-0.64, 0.44]
4 CANTAB Paired Associates Learning (PAL) test	1	136	Mean Difference (IV, Random, 95% CI)	-3.10 [-3.71, -2.49]
5 CANTAB Pattern recognition memory (delayed) test	1	136	Mean Difference (IV, Random, 95% CI)	-0.2 [-0.30, -0.10]
6 Working memory measured by Spatial working memory test	1	136	Mean Difference (IV, Random, 95% CI)	0.4 [-0.24, 1.04]
7 CANTAB Rapid visual information processing test	1	136	Mean Difference (IV, Random, 95% CI)	-11.7 [-15.71, -7.69]
8 CANTAB Reaction time test	1	136	Mean Difference (IV, Random, 95% CI)	9.3 [6.76, 11.84]
9 Episodic memory measured by RAVLT (immediate)	1	137	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.50, 0.10]
10 Speed measured by DSST	1	136	Mean Difference (IV, Random, 95% CI)	-1.4 [-1.70, -1.10]
11 Working memory measured by Spatial working memory test	1	136	Mean Difference (IV, Random, 95% CI)	0.4 [-0.24, 1.04]

Analysis 3.1. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 1 Composite outcome: working memory.

Analysis 3.2. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 2 Composite outcome: learning ability.

Analysis 3.3. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 3 Composite outcome: cognitive efficiency.

Analysis 3.4. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 4 CANTAB Paired Associates Learning (PAL) test.

Analysis 3.5. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 5 CANTAB Pattern recognition memory (delayed) test.

Analysis 3.6. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 6 Working memory measured by Spatial working memory test.

Analysis 3.7. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 7 CANTAB Rapid visual information processing test.

Analysis 3.8. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 8 CANTAB Reaction time test.

Analysis 3.9. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 9 Episodic memory measured by RAVLT (immediate).

Analysis 3.10. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 10 Speed measured by DSST.

Analysis 3.11. Comparison 3 Rosiglitazone plus metformin versus glibenclamide (glyburide) plus metformin, Outcome 11 Working memory measured by Spatial working memory test.

APPENDICES

Appendix 1. Update searches from May 2011 to November 2015

Source	Search strategy	Hits retrieved

(Continued)

1. ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: diabetic OR diabetes OR "type 2" OR "type II"	May 2011: 87
[Last searched for this review on 15 October 2016]		Oct 2014: 5
		Nov 2015: 9
		October 2016: 3
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. exp Diabetes Mellitus, Type 2/ 2. (diabet* adj2 ("2" or "type II")).ti,ab. 3. (DM2 or NIDDM or IIDM).ti,ab. 4. or/1-3 5. (cognit* or memor* or QOL or "quality of life").ti,ab. 6. 4 and 5 7. randomized controlled trial.pt. 8. controlled clinical trial.pt. 9. randomized.ab. 10. placebo.ab. 11. drug therapy.fs. 12. randomly.ab. 13. trial.ab. 14. groups.ab. 15. or/7-14 16. (animals not (humans and animals)).sh. 17. 15 not 16 18. 6 and 17 19. (2008* or 2009* or 2010* or 2011*).ed. 20. 18 and 19	May 2011: 470 Oct 2014: 803 Nov 2015: 294 October 2016: 481
3. Embase 1980 to 2011 week 20 (Ovid SP)	1. exp *non insulin dependent diabetes mellitus/ 2. diabetic obesity/ 3. (diabet* adj2 ("type II" or diabetic obesity)).ti,ab. 4. (DM2 or NIDDM or IIDM).ti,ab. 5. "diabetes mellitus".ti,ab. 6. or/1-5 7. (cogni* or dement* or alzheimer* or memor* or QOL or "quality of life").ti,ab.	May 2011: 358 Oct 2014: 417 Nov 2015: 147 October 2016: 260
[Last searched for this review on 15 October 2016]		

(Continued)

8. 6 and 7
9. clinical trial/
10. double blind procedure/
11. single blind procedure/
12. (random* adj3 (assign* or alloc*)).ti,ab.
13. ((singl* or double* or trebl* or tripl*) and (blind* or mask*)).ti,ab.
14. or/9-13
15. 8 and 14
16. (2008* or 2009* or 2010* or 2011*).em.
17. 15 and 16

4. PsycINFO	1. *Diabetes Mellitus/	May 2011: 53
1806 to May week 3 2011 (Ovid SP)	2. ("type 2" or "type II").ti,ab.	Oct 2014: 59
[Last searched for this review on 15 October 2016]	3. 1 and 2	Nov 2015: 13
	4. (DM2 or NIDDM ir IIDM).ti,ab.	October 2016: 21
	5. ("diabetes mellitus" and "type 2").ti,ab.	
	6. ("diabetes mellitus" and "type II").ti,ab.	
	7. ("type 2 diabet*" or "type II diabet*").ti,ab.	
	8. or/3-7	
	9. (cogn* or dement* or alzheimer* or QOL or "quality of life").ti,ab.	
	10. 8 and 9	
	11. (random* and (alloc* or assign*)).ti,ab.	
	12. ((doubl* or singl* or trebl* or tripl*) adj2 (blind* or mask*)).ti,ab.	
	13. randomi?ed.ti,ab.	
	14. "controlled trial*".ti,ab.	
	15. placebo*.ti,ab.	
	16. or/11-15	
	17. 10 and 16	
5. CINAHL (EBSCOhost)	S1 (MM "Diabetes Mellitus, Non-Insulin-Dependent")	May 2011: 119
[Last searched for this review on 15 October 2016]	S2 TX DM2 OR NIDDM OR IIDM	Oct 2014: 140
	S3 TX "diabetes mellitus type 2"	Nov 2015: 123
	S4 TX "diabetes mellitus type II"	October 2016: 61
	S5 TX "type 2 diabet*" OR "type II diabet*"	

(Continued)

	S6 S1 or S2 or S3 or S4 or S5	
	S7 TX cogni* OR dement* OR alzheimer* OR memor* OR QOL OR "quality of life"	
	S8 S6 and S7	
	S9 EM 2008	
	S10 EM 2009	
	S11 EM 2010	
	S12 EM 2011	
	S13 S9 or S10 or S11 or S12	
	S14 S8 and S13	
	S15 TX random* alloc*	
	S16 TX placebo*	
	S17 (MH "Clinical Trials") OR (MH "Randomized Controlled Trials")	
	S18 TX trial OR RCT	
	S19 S15 or S16 or S17 or S18	
	S20 S14 and S19	
6. Web of Science (1945 to present); plus conference proceedings	Topic=(diabet* OR DM2) AND Topic=(cognit* OR dement*) AND Topic=(random* OR trial OR placebo OR "double-blind*" OR RCT) AND Year Published=(2008-2011)	May 2011:367 Oct 2014: 89 Nov 2015: 502 October 2016: 508
[Last searched for this review on 15 October 2016]	Timespan=All Years.	
7. LILACS (BIREME)	diabet\$ [Words] and demen\$ OR memor\$ OR alzheimer\$ OR cogn \$ [Words] and random\$ OR trial OR placebo OR blind\$ OR mask\$ [Words]	May 2011: 17 Oct 2014: 0 Nov 2015: 0 October 2016: 4
[Last searched for this review on 15 October 2016]		
8. CENTRAL (the Cochrane Library)	#1 diabet*	May 2011: 111
	#2 MeSH descriptor Diabetes Mellitus, Type 2, this term only	Oct 2014: 253
	#3 NIDDM OR "II DM" OR DM2	Nov 2015: 153
	#4 #1 OR #2 OR #3	October 2016: 167
	#5 dement* OR alzhem* OR cognit* OR memor*	
	#6 (#4 AND #5), from 2008 to 2011	
9. Clinicaltrials.gov (www.clinicaltrials.gov)	cognition OR cognitive OR memory OR dementia OR alzheimers OR alzheimer Interventional Studies diabetes OR DMII OR DM2 OR diabetic Adult, Senior received from 01/01/2008 to 06/01/2011	May 2011: 54 Oct 2014: 22 Nov 2015: 6
[Last searched for this review on 15 October 2016]		

(Continued)

October 2016: 48

10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	#1 Diabetes AND dementia = 4 #2 diabetes AND cognition = 29 #3 diabetes AND memory = 9	May 2011: 42 Oct 2014: 26 Nov 2015: 24 October 2016: 5
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[Last searched for this review on 15 October 2016]

TOTAL before de-duplication	May 2011: 1678 Oct 2014: 1206 Nov 2015: 1271 October 2016: 1558
TOTAL after de-dupe and first-assess	May 2011: 43 Oct 2014: 171 Nov 2015: 286 October 2016: 255

Appendix 2. Original search: 2008

On 20 January 2008 the following databases were searched:

CENTRAL (the Cochrane Library): issue 4/2007

Search strategy:

- 1 DIABETES-MELLITUS-NON-INSULIN-DEPENDENT*:ME
- 2 OBESITY-IN-DIABETES*:ME
- 3 ((NIDDM or II DM) or DM2)
- 4 ((#1 or #2 or #3)
- 5 (COGN* or DEMENT* or MEMOR*)
- 6 (#4 and #5)

MEDLINE: 1966-2008/01

Search strategy:

- 1 explode "Diabetes-Mellitus-Type-2"/ all subheadings
- 2 diabet* near ("2" or "type II")
- 3 DM2 or NIDDM or IIDM
- 4 #1 or #2 or #3
- 5 cognit* or memor* or QOL or "quality of life"
- 6 #4 and #5
- 7 (randomized-controlled-trial in PT) or (controlled-trial in PT)
- 8 "Randomized-Controlled-Trials"/ all subheadings

Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia (Review)

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9 random* and (allocat* or assign*)
10 (doubl* or singl* or trebl* or tripl*) near (blind* or mask*)
11 placebo*
12 "Double-Blind-Method" in MIME,MJME
13 cross-over or crossover
14 #7 or #8 or #9 or #10 or #11 or #12 or #13
* 15 #6 and #14

Embase: 1985-2008/01 week 3

Search strategy:

1 "non-insulin-dependent-diabetes-mellitus" / all subheadings
2 "diabetic-obesity" / all subheadings
3 "diabetes mellitus" and ("type 2" or "type II")
4 DM2 or NIDDM or IIDM
5 (typ* "2" or typ* "II") near (diabet* or DM)
6 "diabetes type 2" or "diabetes type II"
7 #1 or #2 or #3 or #4 or #5 or #6
8 cogn* or dement* or alzheimer* or memor* or QOL or "quality of life"
9 #7 and #8
10 explode "clinical-trial" / all subheadings
11 "double-blind-procedure" / all subheadings
12 "single-blind-procedure" / all subheadings
13 alloc*
14 random* and (assign* or alloc*)
15 (singl* or double* or trebl* or tripl*) and (blind* or mask*)
16 #10 or #11 or #12 or #13 or #14 or #15
17 #9 and #16

PsycINFO: 1872-2008/01 week 2

search strategy:

1 "Diabetes-Mellitus" in DE
2 #1 and ("type 2" or "type II")
3 DM2 or NIDDM or IIDM
4 "diabetes mellitus type 2"
5 "diabetes mellitus type II"
6 ("type 2" or "type II") near (diab* or DM)
7 "diabetes type 2" or "diabetes type II"
8 #2 or #3 or #4 or #5 or #6 or #7
9 cogn* or dement* or alzheimer* or QOL or "quality of life"
10 #8 and #9
11 random* and (alloc* or assign*)
12 (doubl* or singl* or trebl* or tripl*) near (blind* or mask*)
13 randomi?ed
14 "controlled trial*"
15 placebo*
16 #11 or #12 or #13 or #14 or #15
17 #10 and #16

CINAHL: 1982-2007/12 week 1

Search strategy:

1 "Diabetes-Mellitus-Non-Insulin-Dependent" / all topical subheadings / all age subheadings
2 DM2 or NIDDM or IIDM
3 "diabetes mellitus type 2" or "diabetes mellitus type II"
4 "diabetes type 2" or "diabetes type II"
5 ("type 2" or "type II") near (diab* or DM)
6 #1 or #2 or #3 or #4 or #5
7 cogn* or dement* or alzheimer* or memor* or QOL or "quality of life"
8 #6 and #7
9 random* near (assign* or alloc*)
10 randomi?ed
11(singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
12 placebo*

13 "controlled trial"
14 #9 or #10 or #11 or #12 or #13
15 #8 and #14

Appendix 3. Hierarchy used to select from instruments measuring the same outcome

Hierarchy used to select from instruments measuring the same outcome

For each outcome described in the protocol, we will apply an outcome specific hierarchy.

For example, if a given study reports 3 different instruments to measure executive function, we will apply the hierarchy to choose the single instrument of which we would extract / pool outcome data. For example, if a study reports data on Stroop Color and Word Test, Raven's Progressive Matrices and the Hong Kong list learning test, we will only extract the data from the Stroop Color and Word Test, which is highest on our hierarchy on executive function. Validated versions of a test in alternative languages will be treated as the same test.

We recognise that the outcomes of interest may be measured with multiple other instruments. Instruments which do not appear on the list were not identified more than once in the sample papers. Data from other instruments will be extracted if no instrument from the list is used in a study. If a study uses more than one such instrument, then we have no a priori preference and reviewers' judgment will be used.

Primary outcome: Global cognitive function

Explanation: the hierarchy is based on the frequencies found below.

Hierarchy	Instruments	Frequency of use in sample papers
1	MMSE or modified MMSE	24
2	modified Telephone Interview for Cognitive Status (TICS-m)	8
3	ADAS-Cog	4
4	Clinical Dementia Rating (CDR) or Clinical Dementia Rating sum of boxes (CDR-SOB)	3
5	Hasegawa's dementia scale (HDS-R) / modified HDS	3

Secondary outcome: Executive function

Hierarchy	Instruments	Frequency of use in sample papers
1	Stroop Color and Word Test, referred to as: Modified Stroop test· Victoria version of Stroop Test· California Older Adult Stroop Test (COAST)· Stroop Color and Word Test	24
2	Trail Making Test B	22
3	WAIS-III Similarities task (WAIS = Wechsler Adult Intelligence Scale)	4
4	WAIS-III Matrices or Matrix Reasoning task	3
4	Task Switching	3
5	Raven's Progressive Matrices	2

Secondary outcome: Speed

Hierarchy	Instruments	Frequency of use in sample papers
1	Trail Making Test, A	20
2	Digit symbol substitution test (DSST)	8
3	WAIS-R referred to as (for example): the Digit Symbol Subtest of the WAIS-R; Digit Symbol and Similarities in Wechsler Adult Intelligence Scale 3rd edition; composite score of the Digit-Symbol Coding subtest of the WAIS-III; Symbol Search subtest of WAIS-III	5
4	Symbol Digit Modalities Test (SDMT)	4
5	Choice reaction time	3
5	Cancellation test	3
5	Finger Tapping Test	3
6	2-choice reaction time test	2
6	a subtest of the Leistungs-Prüf-System 50	2
6	Simple Reaction Time	2

Secondary outcome: Episodic memory

If instruments occurred with the same frequency, then we preferred verbal over visual memory tests. If an instrument includes several episodic memory outcomes, then we preferred recall over recognition and delayed over immediate recall.

Hierarchy	Instruments	Frequency of use in sample papers
1	Rey Auditory Verbal Learning Test (RAVLT)	9
4	Logical Memory subtest of the Wechsler Memory Scale 3rd Edition (WMS-III)	5
5	Visual Reproduction II from Wechsler Memory Scale-Revised (WMS-R)	4
5	Benton Visual Retention Test-Revised 5th Edition (BVRT-R)	4
6	delayed recall of the TICS 10-word list	3
6	California Verbal Learning Test	3
6	Visual Reproduction I from Wechsler Memory Scale-Revised (WMS-R)	3
7	Rivermead Behavioural Memory Test (RBMT)	2

(Continued)

7	Hopkins Verbal Learning Test	2
7	Buschke Selective Reminding test	2
7	Paragraph Recall Test	2
7	Rey Complex Figure Test (RCFT)	2

Secondary outcome: Working memory

Hierarchy	Instruments	Frequency of use in sample papers
1*	Digit Span Test of WAIS-III (composite score calculated as difference between- Forward and Backward)	2
2	Digit Span Test of WAIS-III (Backward Component)	16
3	Digit Span Test of WAIS-III (Forward Component)	14
4	“d2” - Test of Attention	2
4	Self Ordered Pointing Test (SOPT)	2
4	Letter Number Sequencing (LNS) test	2

* The WAIS –III composite instrument is preferred over the single components

Secondary outcome: Verbal fluency

Hierarchy	Instruments	Frequency of use in sample papers
1	Verbal fluency test	27
2	COWAT (Controlled Oral Word Association)	3

Secondary outcome: Semantic memory

Hierarchy	Instruments	Frequency of use in sample papers
1	Boston naming Test	7

WHAT'S NEW

Date	Event	Description
14 June 2017	New citation required but conclusions have not changed	An update search was performed for this review on 15 October 2016. New studies found for inclusion. Conclusions unchanged. Authors changed.
14 June 2017	New search has been performed	An update search was performed for this review on 15 October 2016. Review updated. New studies found for inclusion. Conclusions remained unchanged. Author team has changed.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 4, 2002

Date	Event	Description
24 May 2011	New search has been performed	An update search was performed for this review on 24 May 2011.
10 October 2008	Amended	Converted to new review format.
10 October 2008	New search has been performed	An update search was run in January 2008, which retrieved some studies for consideration by the authors.
21 July 2008	New citation required and conclusions have changed	Substantive amendment.
16 November 2005	New search has been performed	An update search was run in August 2005 but no new studies for inclusion or exclusion were retrieved.

CONTRIBUTIONS OF AUTHORS

AAS: conceived the review, conducted trial selection, participated in completion of the report and writing the final draft.

MCH: conducted trial selection.

RV: coordinated the review process, data extraction, risk of bias assessment, analyses, GRADE assessment, 'Summary of findings' table construction, interpretation of results, participated in completion of the report and writing the final draft.

GM: coordinated the review process, data extraction, risk of bias assessment, analyses, GRADE assessment, 'Summary of findings' table construction, interpretation of results, participated in completion of the report and writing the final draft.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We have updated the methods in the review since the original review in accordance with current Cochrane and Cochrane Dementia and Cognitive Improvement Group guidelines.
- We included 'Summary of findings' tables and a methodological assessment of the quality of evidence with the GRADE methodology.
- We separated blinding of participants and personnel from blinding of outcome assessment.
- We added two new inclusion criteria: we included only trials that assessed a treatment for Type 2 diabetes that was approved by international guidelines; and we required a minimum intervention duration of 12 weeks.
- We specified a method for selecting among multiple scales used in a study to measure the same cognitive domain.
- The authors of the review have changed.

INDEX TERMS

Medical Subject Headings (MeSH)

Carbamates [therapeutic use]; Cause of Death; Cognition Disorders [etiology] [mortality] [*prevention & control]; Diabetes Mellitus, Type 2 [complications] [*drug therapy] [mortality]; Glyburide [therapeutic use]; Hypoglycemic Agents [*therapeutic use]; Memory Disorders [etiology] [prevention & control]; Metformin [therapeutic use]; Piperidines [therapeutic use]; Randomized Controlled Trials as Topic; Rosiglitazone; Thiazolidinediones [therapeutic use]

MeSH check words

Humans