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[Intervention Review]

Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment

Cheow Peng Ooi[1], Seng Cheong Loke[2], Zaitun Yassin[3], Tengku-Aizan Hamid[2]

[1]Endocrine Unit, Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia. [2]Institute of Gerontology, Universiti Putra Malaysia, Serdang, Malaysia. [3]Department of Nutrition and Dietetics, Faculty of Medicine & Health Sciences, University Putra Malaysia, Selangor, Malaysia

Contact: Cheow Peng Ooi, Endocrine Unit, Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor DE, 43400, Malaysia. cpooi07@gmail.com.

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ABSTRACT

Background

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia in which daily function is largely intact. This condition may present an opportunity for research into the prevention of dementia. Carbohydrate is an essential and easily accessible macronutrient which influences cognitive performance. A better understanding of carbohydrate-driven cognitive changes in normal cognition and mild cognitive impairment may suggest ways to prevent or reduce cognitive decline.

Objectives

To assess the effectiveness of carbohydrates in improving cognitive function in older adults with normal cognition or mild cognitive impairment.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group Specialized Register, on 6 April 2012 using the terms: carbohydrates OR carbohydrate OR monosaccharides OR disaccharides OR oligosaccharides OR polysaccharides OR CARBS. ALOIS contains records from all major healthcare databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many trial databases and grey literature sources.

Selection criteria

All randomised controlled trials (RCT) examining the effect of any form of carbohydrates on the cognition or daily functioning of adults aged 55 years or over with normal cognition or MCI.

Data collection and analysis

One review author selected and retrieved relevant articles for further assessment. The remaining authors independently assessed whether any of the retrieved trials should be included. Disagreements were resolved by discussion.

Main results

One study was included. It involved 44 adults aged 60 to 80 years and compared a glucose drink with a saccharin drink, given on only a single occasion. Those receiving the glucose drink were significantly faster in completing the switching condition of the modified Stroop test ($F\ 1, 41 = 10.47$; $P < 0.01$) compared to those receiving the saccharin drink. Participants in the glucose group also showed a significantly

smaller dual-task cost in a computerised test of divided attention compared to the placebo group ($F\ 1, 38 = 8.49$; $P < 0.01$, $\eta^2 = 0.18$). As a glucose drink was administered only once, safety, global function, behaviour disturbance, and activities of daily living were not investigated in the study.

Authors' conclusions

With only one RCT included, there is insufficient evidence to base any recommendations about the use of any form of carbohydrate for enhancing cognitive performance in older adults with normal cognition or mild cognitive impairment. More studies of many different carbohydrates are needed to tease out complex nutritional issues and to further evaluate memory improvement.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence for the use of carbohydrates to improve cognitive performance in older adults with normal or mild cognitive impairment

Carbohydrates consist of sugars, oligosaccharides and polysaccharides. These components are found in a large range of foods and have variable effects on digestion, blood sugar levels, and their impact on health. Despite the evidence accumulated from biological and epidemiological (observational) studies and non-randomised clinical trials, only one randomised, controlled trial could be included in this review. This study had 44 participants. Participants who were given a single glucose drink showed possible momentary enhancement of cognitive performance compared to those given a saccharin drink. A safety assessment was not reported. We need more studies on different types of carbohydrates, particularly those from fruit, vegetable and whole grain sources, for older adults with normal cognition and mild cognitive impairment to understand the role of this nutrient type in the prevention or reduction of cognitive decline.

BACKGROUND

Description of the condition

Cognition encompasses the range of higher brain functional domains that include memory, perception, language, and reasoning. Mild cognitive impairment (MCI) represents an intermediate state of cognitive decline along a continuum of normal to demented (Winblad 2004). In the intermediate state preceding dementia, some memory function falls below the level expected for an individual's education and age but does not noticeably impact daily living. This is in contrast to dementia, which inhibits independent daily functioning (Dodge 2006; McGuire 2006; Morala 2006; Scanlan 2007). In the absence of a cure, the burden dementia places on individuals, families, and communities is a tremendous challenge (Prince 2004; WHO 2003).

The confluence of the increasing prevalence of chronic diseases, the ageing population, and the resulting increase in prevalence of cognitive decline and dementia among older adults is the current concern. Between 2001 and 2010, a 100% increase was projected in cases of dementia in developed countries and a 300% increase in Asia and Asia-Pacific countries (Ferri 2005). Even small reductions in the incidence, or delays in the onset, are likely to have significant effects on the prevalence of dementia and the associated enormous public health burden. Evidence from human epidemiologic studies has shown that one important factor which can influence cognitive performance is the nutritional components of food and patterns of their intake in the diet. While simple carbohydrates such as sucrose (glucose and fructose) may have an immediate effect on cognition, diets high in complex carbohydrates, such as fruits, legumes, vegetables, and cereals, are associated with better cognitive function and a lower risk of dementia in the longer term (Dai 2006; Gu 2010; Hughes 2010; Kang 2006; Morris 2006). In contrast, diets high in fats, both trans and saturated fats, may adversely affect cognition (Eskelinen 2008; Laitinen 2006; Morris 2004).

Description of the intervention

Carbohydrates are essential (Lucas 2000) and easily accessible macronutrients. The important components of carbohydrates found in the diet are simple sugars, oligosaccharides, and polysaccharides (IUPAC 1996). Simple sugars such as sucrose are usually found in processed foods, for example soft drinks and biscuits. These are easily digestible and cause an immediate rise in blood glucose levels. On the other hand, oligo- and polysaccharides are commonly found in fruits, vegetables, whole grains, and dairy foods; and they may have variable times of digestion or indigestibility. Fruits, vegetables, whole grains, and vegetable-enriched diets are also the best nutritional sources of phytonutrients, vitamins, and minerals and hence have important roles in overall health maintenance. Formulary dietary foods containing carbohydrates are also used in medical nutritional therapy.

The impact of acute glucose (simple carbohydrate) ingestion on cognitive performance has received much attention. A substantial body of evidence supports a relationship between glucose availability and changes in cognition. Variable improvements in cognitive tasks, as well as adverse effects of glucose and carbohydrate-rich foods, have been demonstrated in both human and animal models across the age spectrum (Foster 1998; Hall 1989; Manning 1990). Progressive glucoregulatory dysfunction with ensuing hyperglycaemia and hyperinsulinaemia, common among older adults, may occur at least a decade before the presentation of type 2 diabetes mellitus (T2DM) (Shulman 1999). The more consistent improvement of cognitive performance following glucose ingestion in healthy elderly individuals (Hall 1989; Manning 1993 ; Manning 1997) and people with Alzheimer's disease (AD) (Craft 1993; Meneilly 1993) than in healthy young individuals suggests a link between poor memory and deranged glucose regulation. This connection is supported by the decline in glucose metabolic activities in the hippocampus that have been demonstrated with advanced imaging techniques in those at risk of age-related cognitive decline or with MCI (Fouquet 2009; Hunt 2007; Li 2008; Mosconi 2008). For those who showed no progression of cognitive deficits, there was a suggestion of compensatory hypermetabolism of glucose with neuronal disconnection in various regions of the brain connecting to the hippocampus (Fouquet 2009). In addition, the decrease in cognitive deficits reported after improvements in glycaemic control in patients with T2DM supports the argument that metabolic disturbances can contribute to possible reversible cognitive deficits (Cooray 2010; Ryan 2006).

Preliminary cohort studies have demonstrated an association between the Mediterranean diet and a significantly lower risk of incident AD. These studies, with follow-up times of four to seven years, report significant effects with a suggestion of dose-response patterns. Among the important characteristics of the Mediterranean diet are a proportionately high intake of vegetables, legumes, fruits, and cereals. Data for the three studies in the USA were from the cohort of the Washington Heights-Inwood Columbia Aging Project (WHICAP). However, each analysis addressed slightly different outcomes. These were the association between AD and the Mediterranean diet (Scarmeas 2006); the association between the progression from MCI to AD and the Mediterranean diet (Scarmeas 2009a); and the association between AD and the Mediterranean diet combined with physical activity (Scarmeas 2009b).

Sampling techniques were used to minimize selection bias and baseline characteristics were compared according to exposure level. However, details of the selection of participants to the exposure group were not provided in some of the publications. Despite methodological limitations in these three studies, there were fairly consistent results regarding the association between higher compliance with a Mediterranean diet and a significantly lower risk of incident AD. In these studies an informant report was not part of the diagnostic process of AD. However, the association of higher compliance with a Mediterranean diet and a reduced risk of MCI may be influenced by the lack of informant reports (Scarmeas 2006; Scarmeas 2009b) and retrospective application of diagnostic criteria for MCI (Scarmeas 2009a). Studies have demonstrated the discriminative and predictive power of these proxy informant reports in differentiating between MCI and AD (Isella 2006) as well as for increasing the accuracy of a diagnosis of AD (Hancock 2009; Morales 1995). A separate study in a European community did not replicate the finding of an association between adherence to a Mediterranean diet and a reduced risk of dementia (Feart 2009). This was due to a lack of statistical power.

Five cohort studies have suggested a significant protective association between higher amounts of vegetables in the diet

and lower rates of cognitive decline or AD; the association was the strongest for green leafy vegetables (Dai 2006; Gu 2010; Hughes 2010; Kang 2006; Morris 2006). Three studies stated that the participants were non-demented at baseline (Dai 2006; Gu 2010; Morris 2006); the other studies did not provide adequate information about baseline cognitive levels (Kang 2006; Morris 2006). However, most participants were assumed to be non-demented at baseline in the latter studies. Only one study included informant reports in the diagnostic process (Dai 2006). The length of follow up ranged from two to 31.5 years. All the studies used sample selection methods to minimize selection bias. The analyses appear to be generally appropriate and were controlled for relevant potential confounders. Although the results of these studies are consistent in that they suggest a protective effect on cognition associated with eating vegetables, the actual differences in mean scores between the groups are small.

Vegetables, legumes, cereals, fruits, and nuts are potential sources of saccharides. Several saccharides and their glycoforms are found in the brain structure (Albach 2001). Clinical and placebo-controlled studies have reported positive effects of some of these saccharides on cognitive performance over the longer term in younger and middle aged adults (Best 2008; Best 2009; Best 2010; Wang 2004). The intervention studies have included proprietary saccharide supplements and saccharides in the diet. The results from these studies suggest the possibility of functional roles of the saccharides in cognitive performance.

How the intervention might work

Carbohydrates are utilised as energy sources while some are important structural and functional components of the brain. Only glucose has been extensively studied. Many of the mechanisms of carbohydrate utilisation at the molecular level remain unclear.

Several mechanisms by which dietary carbohydrates might influence cognitive function have been proposed. These include the following.

1. Glucose as an energy substrate.
2. Neurotransmitter synthesis.
3. Effects via insulin.
4. Effects via cortisol.
5. Peripheral mechanisms.

1. Glucose as an energy substrate

The brain has a high level of energy consumption but low storage capacity. Distribution of energy resources between the brain and blood is strictly regulated (Fehm 2006; Peters 2004). Glucose is the only substrate for brain metabolism in a non-starved state. Mental function is related to blood glucose levels by a narrow, inverted U-shaped dose-response curve (Parsons 1992). There is a deterioration of cognitive function at either end of the optimal range of blood glucose levels.

2. Neurotransmitter synthesis

A number of neurotransmitters (for example acetylcholine and gamma-aminobutyric acid) are products of glucose metabolism. Besides modulating cognitive function and cortical plasticity (Arendt 1986; Bigl 1998; Schliebs 1996), neurotransmitters play critical physiological roles in controlling cerebral blood flow (Sato 2004) and the sleep-wake cycle (de Leon 1997).

3. Effects via insulin

Insulin is a growth factor for all cells, including neurons in the brain. In healthy brains, insulin is involved in the regulation of various processes such as neuronal survival, energy metabolism, and plasticity associated with learning and memory. Direct positive effects of insulin on cognition are supported by several studies utilising intranasal (Benedict 2010; Reger 2006; Reger 2008), intravenous (Craft 2003; Hallschmid 2010), and intracerebroventricular insulin (Park 2000). In contrast, chemical depletion of insulin in rats reduces the size of the brain and induces neurological changes similar to those seen in AD (Lester-Coll 2006). Elevated adiposity increases peripheral insulin resistance (Luchsinger 2009). In turn, insulin resistance and hyperinsulinaemia cause a reduction in brain insulin (Nelson 2008). The resulting deranged blood glucose levels, as well as the degenerative processes in the brain (Li 2007), may lead to abnormal beta-amyloid peptide formation similar to that found in the brains of patients with AD at post-mortem (de la Monte 2009; Westerman 2002). This may also contribute to the higher risk of dementia, including AD, along the continuum of obesity, metabolic disorders, and T2DM seen in epidemiologic studies (Fitzpatrick 2009; Knopman 2009; Muller 2007; Stewart 2005; Yaffe 2009).

4. Effects via cortisol

The corticosteroid hormone cortisol has also been suggested as a potential mediator of an association between glucose and cognition (Comijs 2010; Huang 2009; Souza-Talarico 2010). Cortisol responses to glucose load are complex and may vary with circumstances. In healthy adults, glucose stimulates cortisol release only during demanding tasks (Gonzalez-Bono 2002). Although glucose ingestion prior to a stressful task specifically provokes a greater cortisol response to the task it is the response on plasma glucose levels that determines the extent of the rise in cortisol (Kirschbaum 1997). In both animal and some human studies there is, as with glucose, evidence for an inverted U-shaped relationship between the cortisol dose and cognitive performance (Abercrombie 2003). There is a deterioration of cognitive function, especially memory, at both ends of the cortisol spectrum. The presence of a high level of cortisol and a raised concentration of cortisol-binding receptors in the hippocampus induces memory impairment (Het 2005; Newcomer 1994). This may explain the association between high morning plasma cortisol levels and raised cortisol following a post-prandial rise in blood glucose with adverse memory performance in patients with impaired glucose tolerance and T2DM (Benton 2003; Reynolds 2010; Rosmond 2000).

5. Peripheral mechanisms

Attenuation of the memory-enhancing effects of peripherally administered hormones following vagotomy in rats suggests that gastrointestinal (GI) hormones (for example cholecystokinin, gastric-releasing peptide, and bombesin) could relay signals to the central nervous system via the vagus nerve to influence cognitive processes (Flood 1987; Flood 1988). Circulating ghrelin, released following the consumption of significant proportions of complex carbohydrates, crosses the blood–brain barrier (Diano 2006) adversely influencing cognitive function (Spitznagel 2010). The extent of the actual effects of all these hormones on the brain is unclear.

Finally, other saccharides, such as mannose, galactose, fucose, xylose, n-acetyl-glucosamine, n-acetyl-neuraminic acid, n-acetyl-

galactosamine, and their glycoforms, are involved in the functioning of synapses and neurotransmitters (Miller 2009; Yamaguchi 2002). They are involved in modulating the electrical activity of neurons (Kleene 2004), the general integrity of the central nervous system (Bandtlow 2000; Maeda 2010), and play a role in mood regulation (Dutton 2008). An involvement of saccharides in cognition is also likely. There is still much to learn of exact mechanisms.

Why it is important to do this review

The predicted acceleration in the demographic shift towards an aged population will result in greater increases in the number of elderly people living in less developed countries, where malnutrition or inappropriate nutrition is more common, compared to developed countries (UN 2007). Furthermore, an anticipated extended lifespan does not imply extended disease-free or disability-free life expectancy as it once did in developed countries, such as Japan (WHO 2003). A better understanding of factors that may prevent or reduce cognitive decline beyond MCI could ease the public burden and enable the development of effective strategies to improve public health.

This review examines the effects of carbohydrates on cognitive performance in both older adults with normal cognition and with MCI. An enhanced understanding of the role of carbohydrates in driving cognitive changes in these groups may suggest future research directions which focus on the relationship between nutrition, the brain, and those cognitive functions which are necessary to sustain independent living.

OBJECTIVES

To assess the effectiveness of carbohydrates in improving cognitive function and the ability to perform activities of daily living.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) were included without restrictions on the basis of language, date of trial, publication status, or duration.
- Two-period crossover studies with randomisation and absence of carryover effects were potentially eligible for inclusion.

Types of participants

Studies of people aged over 55 years, of either gender, who showed no evidence of cognitive impairment or who had mild cognitive impairment and were living in the community (non-institutionalised) were considered.

The diagnosis of mild cognitive impairment (MCI) was based on the consensus criteria of Winblad 2004. These criteria are as follows.

1. Not normal but not demented; do not meet criteria (DSM IV, ICD 10) for a dementia syndrome (APA 1994; ICD 1993).
2. Cognitive decline is determined by self or an informant report; impairment on objective cognitive tasks or evidence of decline over time on objective cognitive tasks.
3. Preserved basic activities of daily living or minimal impairment in complex instrumental functions.

Participants with impaired glucose tolerance and type 2 diabetes mellitus (T2DM) were included. Those with neurological diseases (including in the central nervous system) and on active medications affecting cognition were also excluded. Some examples of active medications affecting cognition are the licensed drugs used in dementia (donepezil, rivastigmine, galantamine, and memantine), benzodiazepines and other sedative-hypnotics, antipsychotic drugs, glucocorticoids, and anticholinergics.

Types of interventions

All forms of intervention with carbohydrates, with or without other nutrients or substances, were considered. Monosaccharide, disaccharide, oligosaccharide, and polysaccharide interventions were eligible. These interventions could be for any time duration. Only the oral mode of administration was considered. Studies with placebo or no intervention comparison groups were eligible for inclusion, though the latter were considered separately. Studies were eligible if the intervention consisted of a provided diet and the comparator was the usual diet. Trials where the intervention was compared to another active intervention and not to a placebo were excluded.

Types of outcome measures

Primary outcomes

The primary outcomes of interest were as follows.

1. Cognitive function: this included any cognitive outcome measure that is sensitive to change in those people with normal cognition or MCI. Such measures may test the individual cognitive domains, a combination of cognitive domains, or overall global function (e.g. Cambridge Cognitive Examination (CAMCOG)).
2. Functional performance: any outcome measures of the activities of daily living, instrumental activities of daily living (IADL), and higher hierarchy of functions were to be included. Examples are Functional Capacities for Activities of Daily Living, or FC-ADL (an error-based ADL measure) (Jefferson 2008), standardised timed IADL measure (Wadley 2008), Everyday Problems Test (a measure of everyday problem solving indexing IADLs) (Burton 2009), global driving ratings (Wadley 2009), and the Financial Capacity Instrument (Triebel 2009).

Secondary outcomes

These outcomes were also considered, if reported:

1. behavioural or affective disorders;
2. quality of life;
3. glycaemic control;
4. safety and adverse effects.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), which is the Cochrane Dementia and Cognitive Improvement Group (CDCIG) Specialized Register (6 April 2012). The search terms used were: carbohydrates OR carbohydrate OR monosaccharides OR disaccharides OR oligosaccharides OR polysaccharides OR CARBS.

ALOIS is maintained by the Cochrane Dementia Group's Trials Search Co-ordinator and contains studies in the areas of dementia prevention, dementia treatment, and cognitive enhancement in healthy people. The studies are identified from the following.

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO, and LILACS.
2. Monthly searches of a number of trials registers: ISRCTN; UMIN (Japan's Trials 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).
3. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*).
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see 'About ALOIS' on the ALOIS website.

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 CDCIG. Additional searches were performed in many of the sources listed above 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. Details of an earlier search for trials to be included in this review can be seen in Appendix 2.

The search of May 2008 retrieved a total of 419 results. After a first assessment and de-duplication of these results, the authors were left with 26 references for further assessment. In June 2010, the search retrieved a total of 1469 results. After a first assessment and de-duplication of these results the authors were left with 39 references to further assess. In the subsequent updated search of April 2012, 1343 results were retrieved. After the first assessment and removal of duplicate publications, 25 references remained for further assessment.

Searching other resources

The electronic search was complemented by a manual search for recent, relevant articles in medical libraries. Reference lists of retrieved articles were also screened for additional trials. Additional relevant information was also searched for using the Internet search engine Google. Three additional references were found from these searches.

Data collection and analysis

Selection of studies

One review author (CPO) discarded obviously irrelevant publications based on the title of the publication and its abstract. In the presence of any suggestion that an article could be relevant, it was retrieved for further assessment. The review authors independently assessed the trials from the resulting culled list for exclusion or inclusion. Full papers were reviewed to resolve queries about data and to clarify questions of concern. One author was contacted for clarification. Disagreements were resolved by discussion between the authors or consultation with a third party.

Data extraction and management

Methodological characteristics of each trial were entered in a table with information on the country of study; the number, age and gender of participants randomised to the groups; the method used to exclude dementia; inclusion and exclusion criteria; the methods of randomisation and allocation concealment; the method of measurement of cognitive performance used in the study; the methods of measurement of outcomes; and the number of participants lost during treatment.

Summary statistics that were reported in each study were to be extracted. For continuous data, this was to be the mean change from baseline, the standard deviation of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation, and the number in each treatment group at each time point were to be extracted. For binary outcomes, the number in each treatment group and the numbers experiencing the outcome of interest or end-point of clinical relevance were to be extracted. Where available, intention-to-treat (ITT) data were to be used. In the absence of ITT data, data for on-treatment analysis were to be extracted, and indicated as such.

Assessment of risk of bias in included studies

Methodological quality criteria were developed, with input from all of the authors, based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). The intention was for two authors to independently assess and score the studies according to the following criteria: method of randomisation; concealment of treatment allocation; similarity of groups at baseline with regard to the most important prognostic indicators; details of eligibility criteria, blinding, presence of point estimates and measures of variability for the primary outcome measures; and the presence of an ITT analysis.

When the description of the randomisation process was unclear or missing, the corresponding author of the study was contacted in an attempt to retrieve the required information. Trials at high risk of bias due to inadequate methods of randomisation or allocation concealment would be excluded. Trials with inadequate concealment have been shown to overestimate the treatment effect (Chalmers 1983; Schulz 1995). Using the recommended approach outlined in Section 8.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.0.2), the risk of bias for important outcomes within and across studies would be included in a summary assessment.

Data analysis

No raw data were available in the report of the included trial. The discussion in subsequent paragraphs is based on the reported analyses.

RESULTS

Description of studies

The CDCIG database search identified 26 trials from the first search in May 2008, 39 trials from the search in June 2010, and a further 25 trials from the search in April 2012. In addition, three trials were identified from other searches. One duplicated study was removed. A total of 92 trials were screened. All of the studies except for two were published in English. After examining the abstracts, full-text

articles were obtained for assessment when it was unclear if the criteria for inclusion were met. Authors from the selected trials were contacted for further details . Only one author replied. These processes are summarised in Figure 1.

Figure 1. Adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection.

Included studies

There was only one published RCT that fulfilled the inclusion criteria (Gagnon 2010). For full details of the trial, see the 'Characteristics of included studies' table. In this between-participants double-blind, randomised controlled trial, a glucose drink was compared with a placebo drink. The intervention consisted of 50 g of glucose mixed with 290 mL of water and 10 mL of lemon juice (Xenex Labs©); while 23.7 mg of saccharin, 290 mL of water, and 10 mL of lemon juice (Hermesetas©) were used to make the placebo drink. Each of the participan ts were tested once with either the intervention drink or the placebo drink.

A total of 44 people who met the protocol criteria were recruited. Inclusion criteria were participants without diabetes as well as medical conditions that could affect cognition and bias data interpretation (for example, absence of general anaesthesia in the past six months; absence of neurological disease, stroke, etc). Participants were excluded if they obtained scores lower than 27 on the mini-mental state examination (MMSE) (Folstein 1975) and if their fasting blood glucose levels were equal to or greater than 7.0 mmol/L. The mean age of the participants was 67.7 years. The glucose group and the placebo group did not differ across age, gender, years of education, body mass index, MMSE, digit span forward, digit span backward, matrix reasoning, and digit symbol substitution at baseline.

Outcome measures

Modified Stroop test

This test was based on the protocol developed by Lezak 1995. The colour- related tests were carried out in four different conditions (reading, naming, inhibition, switching). Under each condition, the participant was given instructions to execute the task as fast and as accurately as possible. The colour reading and naming conditions evaluate the processing speed. Testing the inhibition condition involves naming the colour in which a colour word is printed, and that differs from the original meaning (for example, RED printed in green ink). Alternating between identifying the colour in which the colour word is printed and reading the word when it is placed in a rectangle test flexibility and switching.

Trial making test, part A

This task assessed processing speed and visuo-spatial search. Numbers one to 25 are placed randomly on the testing sheet. The participant is instructed to trace a line linking the numbers in increasing order as fast as possible.

Trial making test, part B

This task measured controlled attention and flexibility. Numbers and letters are placed randomly on a sheet of paper. The participant is instructed to link alternately between letters and numbers, in alphabetical and increasing numerical orders.

Computerised dual-tasks

This consisted of a set of visual discrimination tasks that test the divided attention. E-Prime 1 stimuli were viewed at approximately 45 cm from a personal computer (PC) monitor. Green or yellow colour discrimination tasks and B or C letters discrimination tasks were performed alone and concurrently. In a single-pure trial, one of the tasks was executed consecutively; while in the dual-mixed trial, both tasks were performed concurrently. One of the tasks, single-mixed trial, was presented alone in between the concurrent trials. These trials were used to control for memory load incurred by maintaining different response alternatives as well as to isolate the cost of co-ordinating both tasks. The calculated attentional costs provide information on cognitive processes involved in dual-task situations.

Excluded studies

On screening the 92 trials, there were 71 RCTs and the remaining 21 records were non-randomised or controlled clinical trials. A total of 22 RCTs and 21 non-randomised or controlled clinical trials did not meet any of the selection criteria of this review and were excluded. Of the 49 remaining RCTs, two studies are ongoing (ACTRN12606000475549; NCT01427231 2011). Four full-text articles were retrieved for further assessment. The reasons for exclusion of 46 studies were as follows.

1. Three studies used a counter-balanced crossover design (Riby 2004; Riby 2006; Riby 2009). Random assignment could not be confirmed in any of the three trials. Furthermore, Riby 2004 and Riby 2006 did not use accepted consensus criteria for diagnosis of MCIs and did not use DSM IV (APA 1994) or ICD 10 (ICD 1993) criteria for exclusion of dementia.
2. The participants of 32 studies were either younger than the specified age criterion (Benton 2003; Benton 2004; Best 2008; Best 2010; Brandt 2010; Brinkworth 2009; Cheatham 2009; Corsica 2002; Ford 2002; Halyburton 2007; Kennedy 2004; Lloyd 1994; Maridakis 2009a; Maridakis 2009b; Markus 2007; Markus 2008; Meikle 2004; Morgan 2009; Nabb 2006; NCT00980408; Rohleder 2009; Salinsky 2005; Scholey 2006; Scholey 2009; Smith 2009; Wang 2004; Wells 1998; Winder 1998), were acutely ill patients in hospital (Gariballa 2006; Garriballa 2007), or had dementia on entry to the trial (Ban 1991; Young 2004). ACTRN12610000624088 2010 included patients aged 45 to 60 years but separate data were not available for those aged over 55 years.
3. Two studies used fatty acids, not carbohydrates, for interventions. These were ketasyn, a medium-chain triglyceride (Henderson 2006), and NeoBee 895 (Stepan, Inc.), an emulsified medium-chain triglyceride (Reger 2004).
4. One study used choline alphoscerate, a membrane phospholipid, for intervention (Levin 2009). Another study used tryptophan for intervention (Markus 2006).
5. Two studies used pharmacological agents, repaglinide, glibenclamide (Abbatecola 2009), gluisine, and glargine (Bergenstal 2008), for interventions.
6. In two study, the interventions were ketogenic and non-ketogenic diets of low energy contents (Krikorian 2012; Wing 1995).
7. The primary and secondary end-points of three studies were not cognition or cognitive performance. The primary outcomes of one study were antioxidant biomarkers with no measures of cognition (Amagase 2009). In the second study, the end-points were behaviour changes pertaining to life-styles and not cognition (Block 2008). The participants in the third study had seasonal affective disorder (Mischoulon 2010). There were no exclusion criteria for MCI and dementia as well as no cognitive outcome measures. Another study analysed only the relationship between glycaemic control and cognition (Cukierman-Yaffe 2009).

Ongoing classification

There were two ongoing studies: ACTRN12606000475549 and NCT01427231 2011. Although NCT01427231 2011 fulfilled the inclusion criteria and data collection was complete, no data were available for analysis. Details of the ongoing studies are given in the Table 'Characteristics of ongoing studies'.

Risk of bias in included studies

There was only one RCT included in this review (Gagnon 2010). This study was a between-participants, double-blind, randomised controlled trial. Although the study design was confirmed by the author, no further details were provided. Interventions in both the study and control arm were carried out only once. There were a number of methodological limitations which must be considered. In total, 44 participants (32 women and 12 men) took part in the study. All have an education of a mean of 15.2 years. The inclusion and exclusion criteria are summarised in Characteristics of included studies. Only one participant failed the screening, due to a fasting blood glucose of greater than 7 mmol/L. There were no withdrawals during the trial. Please refer to Figure 2 and Figure 3.

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

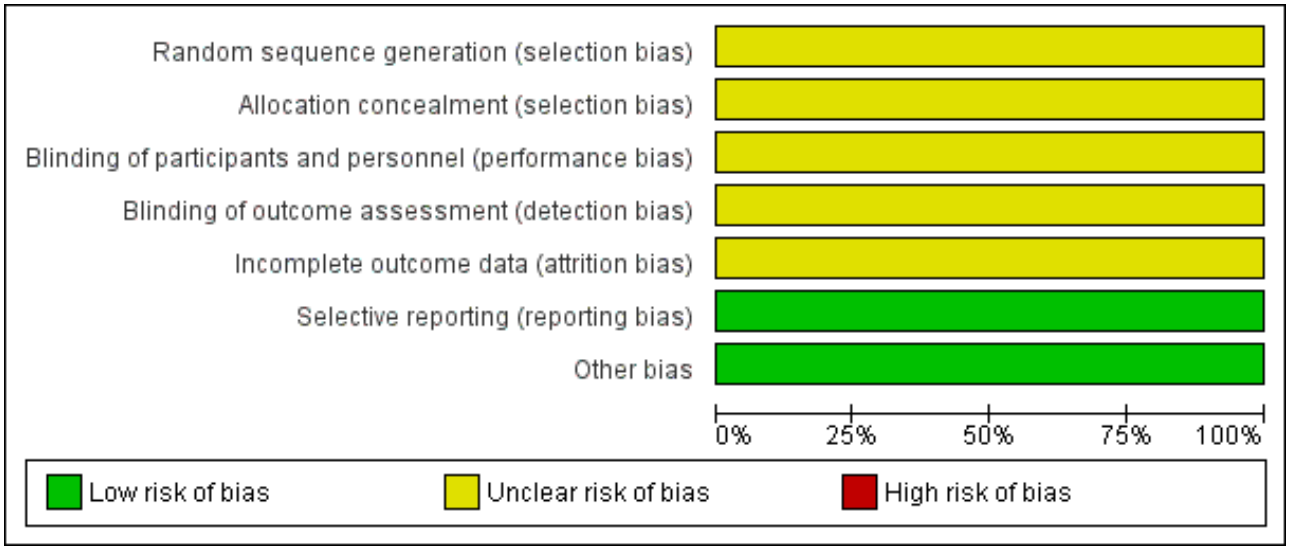
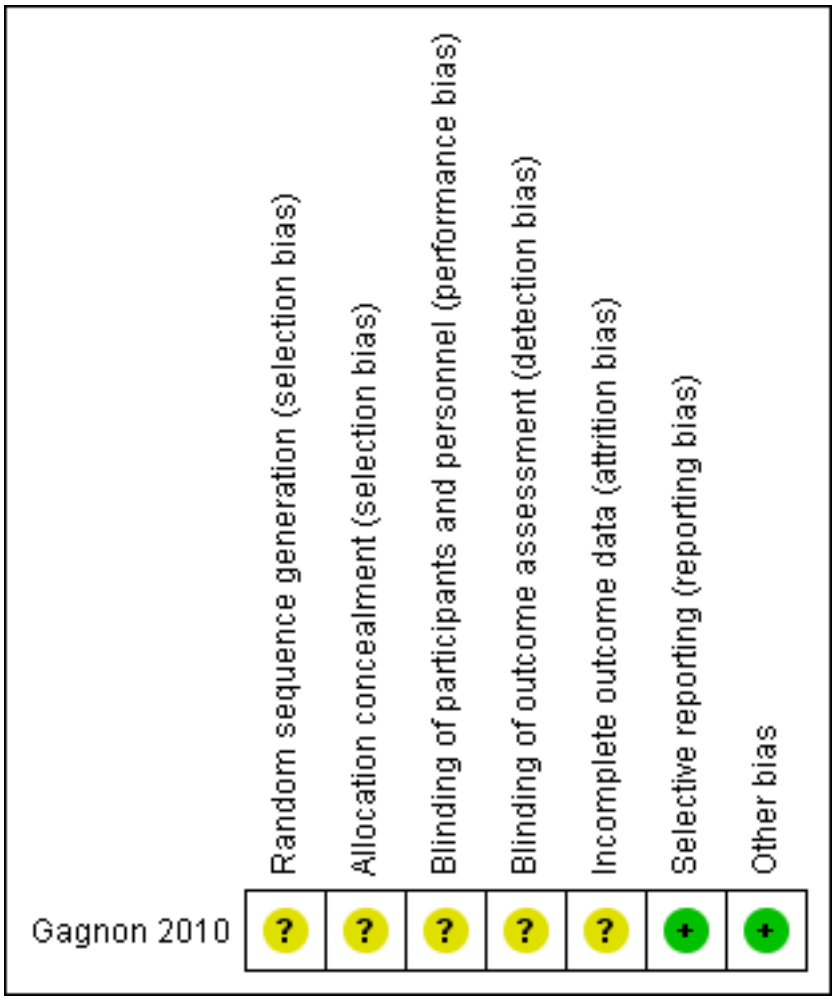


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The study did not report adequately on randomisation and allocation concealment.

Blinding

Although the study was described as double-blinded, there was no reporting of the double-blinding procedure.

Incomplete outcome data

Data were either incomplete or missing in both the glucose and placebo groups. Data were unavailable for one male participant in the computerised task because he was unable to discriminate between the colours green and yellow. Further, one female participant in the glucose group was not able to complete the task. In the trial making tests A and B, one female participant was excluded because she misunderstood the instructions. There was no detail on how these missing data were managed.

Selective reporting

None detected

Other potential sources of bias

None detected

Effects of interventions

Outcomes

Modified Stroop test

This outcome was reported by the authors but no further data were available for detailed examination. Four conditions of the task were included in the analysis and were subjected to two-way analysis of variance with factors of treatment arm. One participant was unable to distinguish colours and was excluded. The glucose arm compared to the placebo arm was significantly faster to complete the switching condition of the modified Stroop test ($F\ 1, 41 = 10.47$; $P < 0.01$). For the three other conditions, there were no significant differences between the two arms. These results corresponded to the analyses for errors. Significant difference in errors between groups were found only on the switching condition ($F\ 1, 41 = 6.26$; $P < 0.05$), with more errors for participants in the placebo group ($M = 4.38$) compared to those in the glucose group ($M = 2.05$). This meant that faster execution times for participants in the glucose group were not accompanied by increased errors.

Trial tests, part A and B

The Trial Making Test consisted of part A and B tasks. There was a significant shorter execution time in the glucose group compared

to the placebo group in the part A task (F 1, 41 = 6.81; P < 0.05). However, there were no significant group differences in the performances of part B as well as both the difference score (B-A) and a ratio score ((B-A)/A). The difference score (B-A) was derived from a calculation to isolate the cost incurred by Trial Making Test, part B. The ratio or proportional score ((B-A)/A)) was derived by controlling for visuo-spatial and speeded components of both parts, A and B.

Computerised dual-tasks

The analysis by the authors showed only a statistically significant smaller dual-task cost for participants in the glucose group on the non-prioritised task when compared to the placebo group (F 1, 38 = 8.49; P < 0.01, η^2 = 0.18). This smaller dual-task cost remained significant when the researchers controlled for speed of processing.

Safety and tolerability

There was no report of adverse effects.

Heterogeneity

Heterogeneity was not assessed in view of only one study being available.

Subgroup analysis

Subgroup analysis was not performed due to insufficient data.

Sensitivity analyses

Sensitivity analyses was not performed due to insufficient studies and data.

Publication and small study bias

A funnel plot was not possible due to insufficient studies and data.

DISCUSSION

There was one study included in this review (Gagnon 2010). In view of the limited availability of studies and data, there is insufficient evidence to confirm the effect of carbohydrates on cognitive function and the ability to perform daily activities in older adults with normal cognition or mild cognitive impairment (MCI). Previous reviews have focused on animal and human experimental trials but not on RCTs.

Any benefits of the short-term or prolonged use of glucose are yet to be established. A high intake of simple carbohydrate, such as sucrose (glucose and fructose), is a risk factor for obesity, metabolic syndrome, and associated impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) (Malik 2010). In turn, obesity, metabolic syndrome, IGT, and T2DM are risk factors for cognitive decline (Gatto 2008; Roriz-Filho 2009). Therefore, interventions containing high proportions of simple carbohydrates may have the potential to exacerbate risk factors for cognitive decline. Further, the association between caloric restrictions and enhancement of memory performance seen in epidemiological observational studies (Beydoun 2008; Wilcox 2007) as well as in an experimental study of ageing brains (Witte 2009) support an adverse effect of prolonged consumption of high levels of simple carbohydrate.

On the other hand, increased total vegetable intake (Dai 2006; Gu 2010; Hughes 2010; Kang 2006; Morris 2006) and adherence to the 'Mediterranean diet' have been associated with reduced risk of dementia (Feart 2009; Scarmeas 2006; Scarmeas 2009a; Scarmeas 2009b; Trichopoulou 2003). Vegetables, legumes, and cereals form major components of the latter diet. These foods are rich in complex carbohydrates such as dietary fibres. Other components of the Mediterranean diet, such as omega-3 fatty acids or flavonoids, may also have neuroprotective benefits. However, not all studies with omega-3-fatty acids have demonstrated benefits for cognition (Kalmijn 1997; Morris 2005; Solfrizzi 2006). Furthermore, though flavonoids have demonstrated effective antioxidant behaviour in cellular models (Stein 2006), the results of preventive clinical trials with vitamin E, an antioxidant, have not found any benefits for cognition and it may even be detrimental (Isaac 2008; Lloret 2009).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of carbohydrates in maintaining or improving cognitive competence, which impacts on independent living in older adults with normal cognition or mild cognitive impairment.

Implications for research

The implications for research are two-fold. First, there is a continuing potential for development of interventions for cognitive enhancement from the diversity of carbohydrate sources that are available. The second is the quality of the available studies.

The wide range of carbohydrates and their many apparent effects on cognitive functions mean that, at first sight, they might appear suitable as interventions to improve failing cognitive function in the elderly. However, identifying an effect of any individual nutrient in healthy diets is challenging because of known synergies between nutrients, the difficulty of controlling and recording dietary intake over a long period, the occurrence of insulin resistance and associated diabetes, as well as the effect of overall nutritional status.

Since evidence available on the protective associations of a Mediterranean diet and high vegetable intake has focused on limited population groups in developed countries, confirmation of these findings in other populations, particularly in Asians, is necessary. Small effect sizes, the inappropriate use of multiple cognitive measures, and the possibility of residual confounders all need to be considered in designing these studies. If a protective association is confirmed, it is necessary to identify potential interventions that are of high impact and cost-effective in reducing the burden of dementia in the coming years. The effectiveness of such interventions at a population versus clinical level needs to be clarified. The impact of co-morbid conditions, the presence of other modifiable risk factors for cognitive decline, and the optimal age for initiation of potential interventions are also among the important issues that need to be addressed.

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CHARACTERISTICS OF STUDIES

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

Gagnon 2010

Methods	This randomised controlled trial (RCT) was of between-subjects design. The methods of randomisation and allocation concealment were not mentioned in the article. The authors had not responded to our query on this matter. Both the participants and investigators were blind to the nature of the drink. Intention-to-treat analysis was not mentioned.
Participants	40 healthy community dwelling adults of both genders aged between 60 and 80 years.

Gagnon 2010 *(Continued)*

	Inclusion criteria: no diabetes as well as medical conditions that could affect cognition and bias data interpretation (e.g., absence of general anaesthesia in the past 6 months, absence of neurological disease, stroke, etc). Exclusion criteria: MMSE (Folstein 1975) less than 27, diabetes, fasting blood glucose levels equal to or greater than 7.0 mmol/L, a history of any medical conditions that could affect cognition (e.g., general anaesthesia in the past 6 months, neurological disease, stroke, etc), unable to complete tasks due to auditory or visual impairments.
Interventions	Each participant received a glucose drink (50 g of glucose mixed with 290 mL of water and 10 mL of lemon juice (Xenex Labs©)) or a placebo drink (23.7 mg of saccharin, 290 mL of water, and 10 mL of lemon juice (Hermesetas©)). Intervention: a glucose drink consisting 50 g glucose mixed with 290 mL of water and 10 mL of lemon juice (Xenex Labs©) Control: a placebo drink consisting of 23.7 mg of saccharin, 290 mL of water, and 10 mL of lemon juice (Hermesetas©). Participants fasted for 10-12 hours prior to the intervention.
Outcomes	Blood glucose level following drink ingestion at 0, 15, 30, 45 and 90 minutes; attentional functions: neuropsychological tests (trail A and B, modified Stroop) and a computerized dual-task.
Stated aims of study	To determine the overall acute effects of glucose ingestion on different forms of attention and attentional control mechanisms in fasting healthy older adults.
Notes	Original research article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although the author confirmed the presence of random sequence generation, further information was not available.
Allocation concealment (selection bias)	Unclear risk	Although the author confirmed the presence of allocation concealment, further information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although the author confirmed the presence of blinding, further information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although the author confirmed the presence of blinding, further information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were either incomplete or missing from the following groups. 1. Data from one male participant in the glucose group as well as one in the placebo group were unavailable for the computerised task because they were unable to discriminate between green and yellow colours. 2. Data from one female participant in the glucose group were also missing because she had not completed the task. There was no information on how these missing data were managed.

Gagnon 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Nothing detected.
Other bias	Low risk	Nothing detected.

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

Study	Reason for exclusion
Abbatecola 2009	Although this was a randomised controlled trial two pharmacological agents, repaglinide and glibenclamide, were the interventions used.
ACTRN12610000624088 2010	The ages of the participants ranged from 45 to 60 years. There is no specific data on participants aged 55 or over for meeting the criteria for inclusion in the systematic review.
Amagase 2009	Although this was a randomised controlled trial, the end-points were antioxidant biomarkers with no cognitive measures.
Ban 1991	Although this was a randomised controlled trial, the participants had dementia.
Benton 2003	Although this was a randomised controlled trial, the participants were young adults and there was no placebo control.
Benton 2004	Although this was a randomised controlled trial, the participants were young adults.
Bergenstal 2008	Although this was a randomised controlled trial two pharmacological agents, glulisine and glargine, were the interventions used. There was no outcome measure of cognition.
Best 2008	Although this was a randomised controlled trial, the mean age of the study sample (N=45) was below 55 (mean age 52.1 ± 5.86 years).
Best 2010	Although this was a randomised controlled trial, the mean age of the study sample (N=109) was below 55. Mean ages for the placebo and treatment groups were 52.44 ± 4.16 and 53.36 ± 4.58 years respectively.
Block 2008	Although this was a randomised controlled trial, behaviour changes pertaining to life-style were the outcome measures and not cognition.
Brandt 2010	The participants were young adults.
Brinkworth 2009	Although this was a randomised controlled trial, the mean age of the study sample (N=106) was below 55 (mean age 50.0 0.8 years).
Cheatham 2009	Although this was a randomised controlled trial, the participants were young adults.
Conti 1989	There was no randomisation and the particpants had dementia. There was also no placebo control.
Corsica 2002	Although this was a randomised controlled trial, the participants were young females of age between 20-45 years.
Craft 1994	There was no randomised allocation sequence.
Cukierman-Yaffe 2009	Although this was a randomised controlled trial, only the relationship between glycaemic control and cognition was analysed.

Study	Reason for exclusion
DeFrance 1997	There was no randomisation and the participants were young adults. The intervention was amino acids.
Finnigan 1998	The participants were young adults. There is inadequate information of randomised allocation of participants.
Fischer 2001	There was no randomisation and the participants were young adults.
Fischer 2002	There was no randomisation and the participants were young adults.
Ford 2002	Although this was a randomised controlled trial, the participants were young adults.
Gariballa 2006	Although this was a randomised controlled trial and of appropriate age, the participants were hospitalised and acutely ill.
Garriballa 2007	Although this was a randomised controlled trial and of appropriate age, the participants were hospitalised and acutely ill.
Halyburton 2007	Although this was a randomised controlled trial, the mean age of the study sample was below 55 years.
Henderson 2006	Although this was a randomised controlled trial, the was no placebo or non-intervention control.
Kaplan 2000	There was no randomisation.
Kaplan 2001	There was no randomisation.
Kennedy 2004	Although this was a randomised controlled trial, the participants were young adults.
Krikorian 2012	The study assessed the potential cognitive benefit of dietary ketosis in older adults with mild memory decline.
Lee 2001	This was not a randomised controlled trial, with no control or non-intervention group.
Levin 2009	Although this was a randomised controlled trial, the intervention was choline alphoscerate (cereton), a membrane phospholipid.
Lloyd 1994	Although this was a randomised controlled trial, the participants were young adults.
Malacco 1992	The intervention was dihydroergocristine.
Maridakis 2009a	Although this was a randomised controlled trial, the participants were young adults.
Maridakis 2009b	Although this was a randomised controlled trial, the participants were young adults.
Markus 1999	Although this was a randomised controlled trial, the participants were young adults and there was no placebo or non-interventional control.
Markus 2002	Although this was a randomised controlled trial, the participants were young adults. In addition, the intervention was alpha-lactalbumin, instead of carbohydrates.
Markus 2006	Although this was a randomised controlled trial, the intervention was dietary tryptophan, instead of carbohydrates.
Markus 2007	Although this was a randomised controlled trial, the participants were young adults.

Study	Reason for exclusion
Markus 2008	Although this was a randomised controlled trial, the participants were young adults. In addition, the interventions were hydrolyzed protein and alpha-lactalbumin whey protein, instead of carbohydrates.
Meikle 2004	Although this was a randomised controlled trial, the participants were young adults.
Messier 2010	There was no randomisation.
Mischoulon 2010	Although this was a randomised controlled trial, the participants had seasonal affective disorder. There were no exclusion criteria for mild cognitive impairment and dementia as well as no cognitive outcome measures.
Morgan 2009	Although this was a randomised controlled trial, the participants were young adults.
Nabb 2006	Although this was a randomised controlled trial, the participants were young adults and there was no placebo or non-interventional control.
NCT00980408	Although this is a randomised ongoing controlled trial, the participants are young adults.
Nilsson 2009	There was inadequate information on randomised allocation of participants in the counterbalanced design.
Pradignac 1995	This was not a randomised controlled trial, with no control or non-intervention group.
Reger 2004	Although this was a randomised controlled trial, the intervention was a medium chain triglyceride.
Riby 2004	Counterbalanced design but no evidence of randomisation.
Riby 2006	Counterbalanced design but no evidence of randomisation.
Riby 2008	There was inadequate information on randomised allocation of participants in the counterbalanced design. The participants were younger than specified age.
Riby 2009	Counterbalanced design but no evidence of randomisation.
Rohleder 2009	Although this was a randomised controlled trial, the participants were young adults. The intervention was oral cortisol and not carbohydrates.
Salinsky 2005	Although this was a randomised controlled trial, the participants were young adults.
Sayegh 1995	There was no randomisation and the participants were young adults.
Scholey 2006	The participants were young adults.
Scholey 2009	Although this was a randomised controlled trial, the participants were young adults.
Smit 2004	There was no randomisation and the participants were young adults.
Smith 2009	There was randomised allocation to groups but the participants were young adults.
Vamosi 1976	There was no randomisation and no control or non-intervention group.
Verger 1998	There was no randomisation and the intervention consisted of protein.
Wang 2004	Although this was a randomised controlled trial, the participants were young adults.

Study	Reason for exclusion
Wells 1998	Although this was a randomised controlled trial, the participants were young adults. The outcome measures were mood, energy expenditure, and heart rate.
Winder 1998	Although this was a randomised controlled trial, the participants were 55 years or less.
Wing 1995	Although this was a randomised controlled trial, the participants were young adults.
Young 2004	Although this was a randomised controlled trial, the participants were from an institution and had probable Alzheimer's dementia.

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

ACTRN12606000475549

Trial name or title	High Protein Diets, Weight Loss and Diabetes Study 2007 Or A 12 week randomised parallel trial comparing 2 different high protein weight loss diets on blood cholesterol levels, blood sugar control and on kidney and cognitive function in Type 2 Diabetes and Obesity: http://www.anzctr.org.au/ACTRN12606000475549.aspx
Methods	Randomised controlled trial, non-blinding
Participants	80 participants with type 2 diabetes mellitus, obesity
Interventions	Two different high protein weight loss diets (12 week dietary intervention of daily high protein 34%, low dietary cholesterol 230mg, fat 26%, carbohydrate 37% diet for 3 meals per day)
Outcomes	Primary outcome measures: low density lipoprotein (LDL); high density lipoprotein (HDL); total cholesterol and triglycerides; fasting ApoB; glucose tolerance test (GTT) (0, 2hours); post-prandial glucose using CGMS (36hr); HbA1C. Secondary outcome measures: nutrient intakes before and during weight loss; plasma folate, homocysteine; cognitive function; satiety profiles; weight loss (including lean and fat loss as assessed by bioelectrical impedance); renal function (urinary urea, plasma creatinine and microalbuminuria); plasma lutein zeaxanthein and other carotenoids.
Starting date	February 2007
Contact information	http://www.anzctr.org.au/ACTRN12606000475549.aspx . 2006
Notes	ongoing

NCT01427231 2011

Trial name or title	Short-term Effect of Glucose and Sacharose Ingestion on Cognitive Performance and Mood in Elderly
Methods	Interventional randomised double-blind crossover controlled trial
Participants	Healthy adults, male and female 70 years and over
Interventions	Interventions: glucose drink or saccharose drink

NCT01427231 2011 *(Continued)*	Control: placebo with sweetener
Outcomes	Primary outcome measures: Performance on the paired associate recall test Secondary outcome measures: 1. Mood, within 90 minutes after consuming the test drink 2. Blood glucose response, from baseline till 90 minutes after consuming the drink 3. Fasting plasma insulin level
Starting date	August 2011
Contact information	NCT01427231
Notes	completed but no publication or data available http://clinicaltrials.gov/ct2/show/NCT01427231

APPENDICES

Appendix 1. Search June 2010

Source	Search strategy	Hits
ALOIS (CDCIG SR) (www.medicine.ox.ac.uk/alois)	Keyword search: carbohydrates OR carbohydrate OR monosaccharides OR disaccharides OR oligosaccharides OR polysaccharides OR CARBS	June 2010: 22 April 2012: 22
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (OvidSP)	1. "cognit* impair*".mp. 2. exp *Cognition Disorders/ 3. MCI.ti,ab. 4. ACMI.ti,ab. 5. ARCD.ti,ab. 6. SMC.ti,ab. 7. CIND.ti,ab. 8. BSF.ti,ab. 9. AAMI.ti,ab. 10. MD.ti,ab. 11. LCD.ti,ab. 12. QD.ti,ab. 13. AACD.ti,ab. 14. MNCD.ti,ab. 15. MCD.ti,ab.	June 2010: 346 April 2012: 281

(Continued)

16. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab.

17. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.

18. "preclinical AD".mp.

19. "pre-clinical AD".mp.

20. ("preclinical alzheimer*" or "pre-clinical alzheimer*").mp.

21. (aMCI or MCIa).ti,ab.

22. ("CDR 0.5" or "clinical dementia rating scale 0.5").ti,ab.

23. ("GDS 3" or "stage 3 GDS").ti,ab.

24. ("global deterioration scale" and "stage 3").mp.

25. "Benign senescent forgetfulness".ti,ab.

26. "mild neurocognit* disorder*".ti,ab.

27. (prodrom* adj2 dement*).ti,ab.

28. (episodic* adj2 memory).mp.

29. ("preclinical dementia" or "pre-clinical dementia").mp.

30. (healthy adj2 (elderly or aged or old* or senior)).mp.

31. "community dwelling".mp.

32. "independent living".mp.

33. (adult* adj2 (old or elderly or aged)).mp.

34. ("healthy participants" or "healthy persons").mp.

35. or/1-34

36. exp Dietary Carbohydrates/

37. exp *Carbohydrates/

38. (carbs or carbohydrate*).ti,ab.

39. Monosaccharides/

40. Disaccharides/

41. Oligosaccharides/

42. Polysaccharides/

43. (monosaccharide* or disaccharide* or oligosaccharide* or polysaccharide*).ti,ab.

44. saccharide*.mp.

45. (sugar* or starch*).ti,ab.

46. or/36-45

47. 35 and 46

48. randomized controlled trial.pt.

(Continued)

	49. controlled clinical trial.pt.	
	50. randomi?ed.ab.	
	51. placebo.ab.	
	52. drug therapy.fs.	
	53. randomly.ab.	
	54. trial.ab.	
	55. groups.ab.	
	56. or/48-55	
	57. (animals not (humans and animals)).sh.	
	58. 56 not 57	
	59. 47 and 58	
	60. (2006* or 2007* or 2008* or 2009* or "2010").ed.	
	61. 59 and 60 [for the 2010 search]	
EMBASE 1980-2010 week 51 (OvidSP)	1. "cognit* impair*".mp. 2. exp cognitive defect/ 3. exp mild cognitive impairment/ 4. MCI.ti,ab. 5. ACMI.ti,ab. 6. ARCD.ti,ab. 7. SMC.ti,ab. 8. CIND.ti,ab. 9. BSF.ti,ab. 10. AAMI.ti,ab. 11. MD.ti,ab. 12. LCD.ti,ab. 13. QD.ti,ab. 14. AACD.ti,ab. 15. MNCD.ti,ab. 16. MCD.ti,ab. 17. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 18. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 19. "preclinical AD".mp. 20. "pre-clinical AD".mp.	June 2010: 524 April 2012: 800

(Continued)

21. ("preclinical alzheimer*" or "pre-clinical alzheimer*").mp.

22. (aMCI or MCIa).ti,ab.

23. ("CDR 0.5" or "clinical dementia rating scale 0.5").ti,ab.

24. ("GDS 3" or "stage 3 GDS").ti,ab.

25. ("global deterioration scale" and "stage 3").mp.

26. "Benign senescent forgetfulness".ti,ab.

27. "mild neurocognit* disorder*".ti,ab.

28. (prodrom* adj2 dement*).ti,ab.

29. "age-related symptom*".mp.

30. (episodic adj2 memory).mp.

31. ("pre-clinical dementia" or "preclinical dementia").mp.

32. (healthy adj2 (elderly or aged or old* or senior)).mp.

33. "community dwelling".mp.

34. "independent living".mp.

35. (adult* adj2 (old or elderly or aged)).mp.

36. ("healthy participants" or "healthy persons").mp.

37. or/1-36

38. exp *carbohydrate/

39. (carbs or carbohydrate*).ti,ab.

40. monosaccharide/

41. disaccharide/

42. oligosaccharide/

43. polysaccharide/

44. saccharide*.mp.

45. (monosaccharide* or disaccharide* or oligosaccharide* or polysaccharide*).ti,ab.

46. (sugar* or starch*).ti,ab.

47. or/38-46

48. 37 and 47

49. randomized controlled trial/

50. controlled clinical trial/

51. randomi?ed.ab.

52. placebo.ab.

53. randomly.ab.

54. trial.ab.

(Continued)

	55. groups.ab. 56. "double-blind*".ti,ab. 57. or/49-56 58. 48 and 57 59. (2008* or 2009* or 2010*).em. 60. 58 and 59	
Psyc INFO 1806-June week 2 2010 (OvidSP)	1. "cognit* impair*".mp. 2. exp Cognitive Impairment/ 3. MCI.ti,ab. 4. ACMI.ti,ab. 5. ARCD.ti,ab. 6. SMC.ti,ab. 7. CIND.ti,ab. 8. BSF.ti,ab. 9. AAMI.ti,ab. 10. MD.ti,ab. 11. LCD.ti,ab. 12. QD.ti,ab. 13. AACD.ti,ab. 14. MNCD.ti,ab. 15. MCD.ti,ab. 16. ("N-MCI" or "A-MCI" or "M-MCI").ti,ab. 17. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab. 18. "preclinical AD".mp. 19. "pre-clinical AD".mp. 20. ("preclinical alzheimer*" or "pre-clinical alzheimer*").mp. 21. (aMCI or MCIa).ti,ab. 22. ("CDR 0.5" or "clinical dementia rating scale 0.5").ti,ab. 23. ("GDS 3" or "stage 3 GDS").ti,ab. 24. ("global deterioration scale" and "stage 3").mp. 25. "Benign senescent forgetfulness".ti,ab. 26. "mild neurocognit* disorder*".ti,ab. 27. (prodrom* adj2 dement*).ti,ab.	June 2010: 90 April 2012: 23

(Continued)

	28. "age-related symptom*".mp. 29. (episodic adj2 memory).mp. 30. ("pre-clinical dementia" or "preclinical dementia").mp. 31. (healthy adj2 (elderly or aged or old* or senior)).mp. 32. "community dwelling".mp. 33. "independent living".mp. 34. (adult* adj2 (old or elderly or aged)).mp. 35. ("healthy participants" or "healthy persons").mp. 36. or/1-35 37. exp Carbohydrates/ 38. (carbs or carbohydrate*).ti,ab. 39. exp *Sugars/ 40. (monosaccharide* or disaccharide* or oligosaccharide* or polysaccharide*).ti,ab. 41. saccharide*.mp. 42. (sugar* or starch*).ti,ab. 43. or/37-42 44. 36 and 43 45. exp Clinical Trials/ 46. random*.mp. 47. placebo.ti,ab. 48. trial.ab. 49. groups.ab. 50. "double-blind*".mp. 51. or/45-50 52. 44 and 51	
CINAHL (EBSCOhost)	S1 TX "cognit* impair*" S2 TX "cognit* defect*" S3 (MH "Cognition Disorders+") S4 TX MCI S5 TX ACMI S6 TX ARCD S7 TX SMC S8 TX CIND	June 2010: 132 April 2012: 0

(Continued)

S9 TX BSF

S10 TX AAMI

S11 AB MD

S12 AB LCD

S13 AB QD OR "questionable dementia"

S14 TX AACD

S15 TX MNCD

S16 TX "N-MCI" or "A-MCI" or "M-MCI"

S17 TX "preclinical AD"

S18 TX "pre-clinical AD"

S19 TX "preclinical alzheimer*" or "pre-clinical alzheimer*"

S20 TX aMCI OR MCIa

S21 TX "CDR 0.5" or "clinical dementia rating scale 0.5"

S22 TX "GDS 3" OR "stage 3 GDS"

S23 TX "global deterioration scale" AND "stage 3"

S24 TX "Benign senescent forgetfulness"

S25 TX "mild neurocognit* disorder*"

S26 TX prodrom* N2 dement*

S27 TX "age-related symptom*"

S28 TX cognit* N2 deficit*

S29 TX cognit* N2 deteriorat*

S30 TX cognit* N2 declin*

S31 TX cognit* N2 degenerat*

S32 TX cognit* N2 complain*

S33 TX cognit* N2 disturb*

S34 TX cognit* N2 disorder*

S35 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or TX memory N2 complain*

S36 TX memory N2 disturb* or TX memory N2 disorder* or TX cerebr* N2 impair* or TX cerebr* N2 los*

S37 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb*

S38 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat*

S39 TX "pre-clinical dementia" or TX "preclinical dementia"

S40 TX healthy N2 elderly

(Continued)

	S41 TX healthy N2 old*
	S42 TX healthy N2 aged
	S43 TX healthy N2 senior
	S44 TX adult N2 old*
	S45 TX adult N2 elderly
	S46 TX adult N2 aged
	S47 TX "community dwelling"
	S48 TX "independent living"
	S49 TX "healthy participants" OR "healthy persons"
	S50 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49
	S51 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49
	S52 TX carbs OR carbohydrate*
	S53 (MH "Monosaccharides") or (MH "Disaccharides") or (MH "Oligosaccharides")
	S54 TX monosaccharide* or disaccharide* or oligosaccharide* or polysaccharide*
	S55 TX saccharide*
	S56 TX sugar* or starch*
	S57 S51 or S52 or S53 or S54 or S55 or S56
	S58 S50 and S57
	S59 (MH "Clinical Trials+")
	S60 AB random*
	S61 AB trial
	S62 AB placebo
	S63 AB "control group"
	S64 AB "double-blind*"
	S65 S59 or S60 or S61 or S62 or S63 or S64
	S66 S58 and S65
Web of Science with Conference Proceedings (1945 to present) (Web of Knowledge)	#1 Topic=(mci OR "mild cognitive impairment")	June 2010: 135 April 2012: 37

(Continued)

	Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S Timespan=All Years *#2* Topic=(aami OR "age associated memory impairment") #3 Topic=("minor memory complaint*" OR aacd OR "age related memory impairment" OR "age associated cognitive decline") #4 Topic=("age related cognitive decline" OR "cognit* impair*") #5 Topic=("cind" OR "smc" OR "subjective memory complaint*") #6 Topic=("preclinical ad" OR "pre-clinical ad" OR "preclinical alzheimer*" OR "pre-clinical alzheimer*") #7 Topic=("episodic memory" OR "dementia prodrome" OR "incipient dementia") #8 Topic=("prevent* dement*" OR "prevent* alzheimer*") #9 Topic=((cognit* OR memory* OR cerebral OR "cognit* function*" OR "brain activity") NEAR (improv* OR enhanc* OR perform* OR process* OR "lessen deterioration")) #10 Topic=(carbohydrate* OR monosaccharide* OR disaccharide* OR oligosaccharide* OR polysaccharide* OR saccharide*) #11 Topic=("double-blind*" OR random* OR "clinical trial" OR placebo) #12 #9 OR #8 OR #7 OR #6 OR #4 OR #3 OR #2 OR #1 #13 #12 AND #10 #14 #13 AND #11	
LILACS (BIREME)	(mci OR "mild cognitive impairment" OR "aami" OR "age associated memory impairment$" OR "minor memory complaint$" OR "aacd" OR "age related memory impairment" OR "age associated cognitive decline" OR "mc la" OR "cognit$ impair$" OR healthy OR elderly OR "cind" OR "smc" OR "subjective memory complaint$" OR "preclinical ad" OR "pre-clinical ad" OR "preclinical alzheimer$" OR "pre-clinical alzheimer$" OR ((cognit$ OR memory$ OR cerebral OR "cognit$ function$" OR "brain activity") AND (improv$ OR enhanc$ OR perform$ OR process$ OR "lessen deterioration"))) [Palavras] and (carbohydrate$ OR monosaccharide$ OR disaccharide$ OR oligosaccharide$ OR polysaccharide$ OR sugar$ OR starch$)	June 2010: 59
CENTRAL (*The Cochrane Library*)	#1 "cognit* impair*" #2 MeSH descriptor Cognition Disorders explode all trees #3 MCI #4 ACMI #5 ARCD #6 SMC #7 CIND #8 BSF #9 AAMI #10 LCD	June 2010: 102 April 2012: 104

(Continued)

#11 QD OR "questionable dementia"

#12 AACD

#13 MNCD

#14 MCD

#15 "N-MCI" or "A-MCI" or "M-MCI"

#16 (cognit* or memory or cerebr* or mental*) NEAR/3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)

#17 "preclinical AD"

#18 "pre-clinical AD"

#19 "preclinical alzheimer*" or "pre-clinical alzheimer*"

#20 aMCI OR MCIa

#21 "CDR 0.5" OR "clinical dementia rating scale 0.5"

#22 "GDS 3" OR "stage 3 GDS"

#23 "global deterioration scale" AND "stage 3"

#24 "Benign senescent forgetfulness"

#25 "mild neurocognit* disorder*"

#26 (prodrom* NEAR/2 dement*)

#27 episodic* NEAR/2 memory

#28 "preclinical dementia" OR "pre-clinical dementia"

#29 episodic NEAR/2 memory

#30 "pre-clinical dementia" OR "preclinical dementia"

#31 (healthy NEAR/2 (elderly or aged or old* or senior))

#32 "community dwelling"

#33 "independent living"

#34 "healthy participants" OR "healthy persons"

#35 MeSH descriptor Carbohydrates explode all trees

#36 carbs or carbohydrate*

#37 MeSH descriptor Monosaccharides, this term only

#38 MeSH descriptor Disaccharides, this term only

#39 MeSH descriptor Oligosaccharides, this term only

#40 MeSH descriptor Polysaccharides explode all trees

#41 monosaccharide* OR disaccharide* OR oligosaccharide* OR polysaccharide*

#42 saccharide*

#43 sugar* OR starch*

(Continued)

	#44 (#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43) #45 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34) #46 (#45 AND #44), from 2008 to 2010	
Clinicaltrials.gov	Interventional Studies | cognitive OR cognition OR elderly OR aged OR memory | carbohydrates OR Monosaccharides OR Disaccharides OR Oligosaccharides OR Polysaccharides | received from 01/01/2008 to 06/22/2010	June 2010: 37 April 2012: 53
ICTRP Search Portal (WHO)	Advanced search: Interventional Studies | cognitive OR cognition OR elderly OR aged OR memory | carbohydrates OR Monosaccharides OR Disaccharides OR Oligosaccharides OR Polysaccharides | received from 01/01/2008 to 22/06/2010	June 2010: 22 April 2012: 21
Total		June 2010: 1469 April 2012: 1343
Total after first-assess		June 2010: 40 April 2012: 25

Appendix 2. Search May 2008

Source searched	Search strategy	Hits after first assess
MEDLINE (OvidSP)	1. (mci or "mild$ cognit$ impair$").mp. 2. ("aa mi" or "age-associated memory impairment").mp. 3. "minor memory complaint$".mp. 4. ("aa cd" or "age related memory impairment" or "age-associated cognitive decline").mp. 5. ("age related" adj3 "cognitive decline").mp. [mp=title, original title, abstract, name of substance word, subject heading word] 6. ("mc la" or "cognit$ impair$").mp. 7. ("ci nd" or "smc" or "subjective memory complaint$").mp. 8. ("preclinical ad" or "pre-clinical ad" or "preclinical alzheimer$" or "pre-clinical alzheimer$").mp. 9. "episodic memory".mp. 10. "dementia prodrome".mp. 11. "incipient dementia".mp. 12. ("prevent$ dement$" or "prevent$ alzheimer$").mp. 13. ((cognit$ or memory$ or cerebral or "cognit$ function$" or "brain activity") adj4 (improv$ or enhanc$ or perform$ or process$ or "lessen deterioration")).mp. 14. alzheimer disease/pc or dementia/pc 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16. Carbohydrates/ or carbohydrate$.mp. 17. Monosaccharides/ or monosaccharide$.mp. 18. disaccharide$.mp. or Disaccharides/ 19. oligosaccharide$.mp. or Oligosaccharides/ 20. Polysaccharides/ or polysaccharide$.mp. 21. 16 or 17 or 18 or 19 or 20 22. 15 and 21 23. randomized controlled trial.pt. 24. controlled clinical trial.pt. 25. randomized.ab. 26. placebo.ab. 27. drug therapy.fs. 28. randomly.ab. 29. trial.ab. 30. groups.ab. 31. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 32. humans.sh. 33. 31 and 32 34. 22 and 33	48
EMBASE (OvidSP)	1. (mci or "mild$ cognit$ impair$").mp. 2. ("aa mi" or "age-associated memory impairment").mp. 3. "minor memory complaint$".mp. 4. ("aa cd" or "age related memory impairment" or "age-associated cognitive decline").mp. 5. ("age related" adj3 "cognitive decline").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 6. ("mc la" or "cognit$ impair$").mp. 7. ("ci nd" or "smc"	38

(Continued)

	or "subjective memory complaint$").mp. 8. ("preclinical ad" or "pre-clinical ad" or "preclinical alzheimer$" or "pre-clinical alzheimer$").mp. 9. "episodic memory".mp. 10. "dementia prodrome".mp. 11. "incipient dementia".mp. 12. ("prevent$ dement$" or "prevent$ alzheimer$").mp. 13. ((cognit$ or memory$ or cerebral or "cognit$ function$" or "brain activity") adj4 (improv$ or enhanc$ or perform$ or process$ or "lessen deterioration")).mp. 14. alzheimer disease/pc or dementia/pc 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16. Carbohydrates/ or carbohydrate$.mp. 17. Monosaccharides/ or monosaccharide$.mp. 18. disaccharide$.mp. or Disaccharides/ 19. oligosaccharide$.mp. or Oligosaccharides/ 20. Polysaccharides/ or polysaccharide$.mp. 21. 16 or 17 or 18 or 19 or 20 22. 15 and 21 23. (random$ or factorial$).mp. 24. (cross over$ or crossover$).mp. 25. placebo$.mp. 26. (doubl$ adj5 blind$).mp. 27. (singl$ adj5 blind$).mp. 28. (assign$ or allocat$ or volunteer$).mp. 29. crossover-procedure/ or dounble-blind procedure/ or single-blind procedure/ 30. randomized controlled trial/ 31. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 32. 22 and 31	
PsycINFO (OvidSP)	1. (mci or "mild$ cognit$ impair$").mp. 2. ("aa mi" or "age-associated memory impairment").mp. 3. "minor memory complaint$".mp. 4. ("aa cd" or "age related memory impairment" or "age-associated cognitive decline").mp. 5. ("age related" adj3 "cognitive decline").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 6. ("mc la" or "cognit$ impair$").mp. 7. ("ci nd" or "smc" or "subjective memory complaint$").mp. 8. ("preclinical ad" or "pre-clinical ad" or "preclinical alzheimer$" or "pre-clinical alzheimer$").mp. 9. "episodic memory".mp. 10. "dementia prodrome".mp. 11. "incipient dementia".mp. 12. ("prevent$ dement$" or "prevent$ alzheimer$").mp. 13. ((cognit$ or memory$ or cerebral or "cognit$ function$" or "brain activity") adj4 (improv$ or enhanc$ or perform$ or process$ or "lessen deterioration")).mp. 14. alzheimer disease/pc or dementia/pc 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16. Carbohydrates/ or carbohydrate$.mp. 17. Monosaccharides/ or monosaccharide$.mp. 18. disaccharide$.mp. or Disaccharides/ 19. oligosaccharide$.mp. or Oligosaccharides/ 20. Polysaccharides/ or polysaccharide$.mp. 21. 16 or 17 or 18 or 19 or 20 22. 15 and 21 23. random$.tw. 24. factorial$.tw. 25. crossover$.tw. 26. cross over$.tw. 27. placebo$.tw. 28. (doubl$ adj blind$).tw. 29. (sing$ adj blind$).tw. 30. Clinical Trials/ 31. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 32. 31 and 22	13
CINAHL (OvidSP)	1. (mci or "mild$ cognit$ impair$").mp. 2. ("aa mi" or "age-associated memory impairment").mp. 3. "minor memory complaint$".mp. 4. ("aa cd" or "age related memory impairment" or "age-associated cognitive decline").mp. 5. ("age related" adj3 "cognitive decline").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 6. ("mc la" or "cognit$ impair$").mp. 7. ("ci nd" or "smc" or "subjective memory complaint$").mp. 8. ("preclinical ad" or "pre-clinical ad" or "preclinical alzheimer$" or "pre-clinical alzheimer$").mp. 9. "episodic memory".mp. 10. "dementia prodrome".mp. 11. "incipient dementia".mp. 12. ("prevent$ dement$" or "prevent$ alzheimer$").mp. 13. ((cognit$ or memory$ or cerebral or "cognit$ function$" or "brain activity") adj4 (improv$ or enhanc$ or perform$ or process$ or "lessen deterioration")).mp. 14. alzheimer disease/pc or dementia/pc 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16. Carbohydrates/ or carbohydrate$.mp. 17. Monosaccharides/ or monosaccharide$.mp. 18. disaccharide$.mp. or Disaccharides/ 19. oligosaccharide$.mp. or Oligosaccharides/ 20. Polysaccharides/ or polysaccharide$.mp. 21. 16 or 17 or 18 or 19 or 20 22. 15 and 21 23. random$.tw. 24. factorial$.tw. 25. crossover$.tw. 26. cross over$.tw. 27. placebo$.tw. 28. (doubl$ adj blind$).tw. 29. (sing$ adj blind$).tw. 30. Clinical Trials/ 31. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 32. 31 and 22	4

(Continued)

LILACS (Bireme)	(mci OR "mild cognitive impairment" OR "aa mi" OR "age associated memory impairment$" OR "minor memory complaint$" OR "aa cd" OR "age related memory impairment" OR "age associated cognitive decline" OR "mc la" OR "cognit$ impair$" OR "ci nd" OR "smc" OR "subjective memory complaint$" OR "preclinical ad" OR "pre-clinical ad" OR "preclinical alzheimer$" OR "preclinical alzheimer$" OR ((cognit$ OR memory$ OR cerebral OR "cognit$ function$" OR "brain activity") AND (improv$ OR enhanc$ OR perform$ OR process $ OR "lessen deterioration"))) [Palavras] and (carbohydrate$ OR monosaccharide$ OR disaccharide$ OR oligosaccharide$ OR polysaccharide$)	3
The Cochrane Library	#1. mci OR "mild cognitive impairment" #2. "aa mi" OR "age-associated memory impairment" #3. "aa cd" OR "age-related memory impairment" OR "age-associated cognitive decline" OR "age-related cognitive decline" #4. "mc la" OR "cognit* impair*" #5. "ci nd" OR "smc" OR "subjective memory complaint*" #6. "preclinical ad" OR "pre-clinical ad" OR "preclinical alzheimer*" OR "preclinical alzheimer*" #7. "episodic memory" OR "dementia prodrome" OR "incipient dementia" #8. "prevent* dement*" OR "prevent* alzheimer*" #9. ((cognit* OR memory* OR cerebral OR "cognit* function*" OR "brain activity") NEAR (improv* OR enhanc* OR perform* OR process* OR "lessen deterioration")) #10. Carbohydrates (MeSH) #11. Monosaccharides (MeSH) #12. Disaccharides (MeSH) #13. Oligosaccharides (MeSH) #14. Polysaccharides (MeSH) #15. Carbohydrate* (Search all Text) #16. Monosaccharides (Search all Text) #17. Disaccharides (Search all Text) #18. Oligosaccharides (Search all Text) #19. Polysaccharides (Search all Text) #20. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 #21. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 #22. #20 AND #21	27
CDCIG Specialized Register	carbohydrates OR monosaccharides OR disaccharides OR oligosaccharides OR polysaccharides	7
ISI Conference Proceedings	#1. Topic=(mci OR "mild cognitive impairment") #2. Topic=("aa mi" OR "age associated memory impairment")	136

(Continued)

	#3. Topic=("minor memory complaint*" OR "aa cd" OR "age related memory impairment" OR "age associated cognitive decline") #4. Topic=("age related cognitive decline" OR "mc la" OR "cognit* impair*") #5. Topic=("ci nd" OR "smc" OR "subjective memory complaints") #6. Topic=("preclinical ad" OR "pre-clinical ad" OR "preclinical alzheimer*" OR "pre-clinical alzheimer*") #7. Topic=("episodic memory" OR "dementia prodrome" OR "incipient dementia") #8. Topic=("prevent* dement*" OR "prevent* alzheimer*") #9. Topic=(((cognit* OR memory* OR cerebral OR "cognit* function*" OR "brain activity") NEAR (improv* OR enhanc* OR perform* OR process* OR "lessen deterioration"))) #10. Topic=(carbohydrate* OR monosaccharide* OR disaccharide* OR oligosaccharide* OR polysaccharide*) #11. Topic=("randomized controlled trial" OR "randomised controlled trial" OR "clinical trial") #12. #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 #13. #12 AND #11 AND #10	
ClinicalTrials.gov	(carbohydrates OR monosaccharides OR disaccharides OR oligosaccharides OR polysaccharides) AND (cognition OR "mild cognitive impairment" OR "age-associated memory impairment" OR "age-related memory impairment" OR "age-associated cognitive decline" OR "age-related cognitive decline" OR "cognitive impairment not dementia" OR "subjective memory complaints" OR "preclinical AD" OR "pre-clinical AD" OR "preclinical Alzheimer" OR "episodic memory" OR "dementia prodrome" OR "incipient dementia")	1
metaRegister of Controlled Trials: ISRCTN Register Action Medical Research Medical Research Council (UK) HTA NIH The Wellcome Trust UK Clinical Trials Gateway	(carbohydrate% OR monosaccharides OR disaccharides OR oligosaccharides OR polysaccharides) AND (cognit% OR "mild cognitive impairment" OR "age-associated memory impairment" OR "age-related memory impairment" OR "age-associated cognitive decline")	168

WHAT'S NEW

Date	Event	Description
6 April 2012	New search has been performed	An update search was performed for this review on 6 April 2012

HISTORY

Protocol first published: Issue 3, 2008
Review first published: Issue 4, 2011

Date	Event	Description
22 June 2010	New search has been performed	1st Updated search
25 April 2008	Amended	First search

CONTRIBUTIONS OF AUTHORS

CPO: drafting of review, search for trials, obtaining copies of trial reports, selection of trials for inclusion or exclusion, extraction of data, entry of data (into RevMan), interpretation of data analyses

ZY: selection of trials for inclusion or exclusion, extraction of data, entry of data (into RevMan)

HT-A: searching for trials, interpretation of data analysis

LSC: searching for trials, obtaining copies of trial reports, selection of included trials and exclusion of trials, extraction of data, interpretation of data analysis

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Institute of Gerontology, University Putra Malaysia, Malaysia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Our approach to data collection and extraction was revised based on the methodology in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.0.2).

INDEX TERMS

Medical Subject Headings (MeSH)

*Cognition; Cognition Disorders [*drug therapy]; Dietary Carbohydrates [*therapeutic use]; Independent Living

MeSH check words

Aged; Humans