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Special Article

Effect of glucose and sucrose on cognition in healthy humans: a systematic review and meta-analysis of interventional studies

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[1]

Context: *Evidence suggests that plasma glucose levels may influence cognitive performance, but this has not been systematically reviewed and quantified.* ***Objective:*** *The aim of this review was to investigate the potential effects of glucose and sucrose, compared with placebo, on cognition in healthy humans.* ***Data Sources:*** *The electronic databases PubMed and Web of Science were searched up to December 2019. Reference lists of selected articles were checked manually.* ***Study Selection:*** *Randomized controlled trials or crossover trials that compared glucose or sucrose with placebo for effects on cognition were eligible.* ***Data Extraction:*** *Potentially eligible articles were selected independently by 2 authors. Risk of bias was assessed through the Cochrane Collaboration tool. Standardized mean differences (SMDs) were obtained from random-effects meta-analyses for a subsample of studies that reported the same outcomes.* ***Results:*** *Thirty-seven trials were identified, of which 35 investigated the effect of glucose consumption compared with placebo on cognition. Two studies found no effect of glucose on cognition, while the others found mixed results. Only 3 of the 37 studies investigated the effects of sucrose intake, reporting mixed results. Meta-analyses revealed a significantly positive effect of glucose compared with control, but only when a verbal performance test (immediate word recall) was used in parallel-design studies (SMD = 0.61; 95%CI, 0.20–1.02; $I^2 = 0\%$). Twenty-four studies were classified as having high risk of bias for the selection procedure.* ***Conclusions:*** *A limited body of evidence shows a beneficial effect of glucose in individuals performing immediate verbal tasks. High-quality trials with standardized cognitive measurements are needed to better establish the effect of glucose or sucrose on cognition.*

Systematic Review Registration: *PROSPERO registration number CRD42019122939.*

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INTRODUCTION

Glucose is the main source of energy for the human brain and plays an essential role in the modulation of cognitive processes. Glucose levels can be increased by direct intake of either glucose, a monosaccharide sugar unit, or sucrose, a disaccharide sugar unit made of glucose and fructose and commonly known as table sugar.[1] It has been suggested that sucrose can have a direct effect on the brain through its glucose component, as well as a peripheral effect through its fructose component,[2] likely because this sugar is first metabolized by the liver before it can be utilized by the brain.[3,4] The brain is sensitive to short-term drops in blood glucose levels and seems to respond positively when blood glucose rises, especially when individuals perform more intense cognitive tasks. This response may be attributable to increased absorption of glucose in the brain.[5]

On the other hand, chronic excessive consumption of sugar is known to contribute to cognitive and memory deficits and to increase the risk of psychiatric disorders in younger populations,[6] an effect also described in observational studies in adults.[7,8] More recently, it has been suggested that sugar-containing drinks can have an adverse impact on children's cognition, while fruit consumption can lead to an improvement in cognition.[9] The biggest drawback of high-glucose intake, however, is the increased risk of chronic diseases, including obesity, fatty liver, dyslipidemia, type 2 diabetes, and cardiovascular disorders, which may develop independently of body weight or energy intake.[10] It is well established that obesity and its comorbidities are associated with impaired cognitive performance, accelerated cognitive decline, and neurodegenerative pathologies.[11] Recent research has also shown that weight loss resulting from a Mediterranean dietary pattern, which is characterized by a high intake of complex carbohydrates but a low intake of sucrose,[12] can improve cognitive performance in people with obesity.[13]

The debate about the role of sugar in brain performance continues, and some works have described deleterious effects of sugar on cognition. Kenny[14] reported that sugar activates the same brain pathways as cocaine or other addictive drugs. Similarly, a report of Ochoa et al[15] showed that glucose and fructose, but not starch, were able to increase basal cerebral glucose metabolism in reward-related brain regions such as the anterior and dorsolateral prefrontal cortex and the orbitofrontal cortex, among others. In contrast, a beneficial effect of glucose loads on cognitive function, particularly episodic memory, was suggested.[16] However, intake of total sugars, added sugars, sucrose, and added fructose has been inversely associated with cognitive performance.[17]

A few previous reviews have analyzed the effect of glucose on different aspects of brain functioning. Beilharz et al[18] reported that the intake of refined sugars was associated with impaired memory tasks in both prospective cohort and cross-sectional studies. In contrast, a comprehensive research review performed in 2011 by Smith et al[19] described an enhancement of human memory after glucose ingestion in interventional studies. In their recent systematic review of interventional studies, van de Rest et al[1] described inconsistent effects of glucose ingestion on mood, but information on cognitive performance was not presented.[1] Thus, to date, evidence on the effect of sugar on brain function has been contradictory. To the best of knowledge, no previous meta-analysis has evaluated the association between glucose consumption and cognition, and no review or meta-analysis has compared the different effects, if any, of glucose and sucrose on cognition. The aim of this systematic review and meta-analysis was to investigate and quantify the potential effects of glucose and sucrose, compared with placebo, on cognition in healthy adults.

METHODS

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed.[20] The PRISMA checklist is provided as Table S1 in the Supporting Information online). The systematic review was registered on the PROSPERO database (registration no. CRD42019122939).

Data sources and literature search

The PubMed database was searched for suitable articles published up to June 2019. The following MeSH (Medical Subject Headings) search terms were used: ("glucose"[All Fields] OR "sucrose"[All Fields] OR "fructose"[All Fields] OR "sugar"[All Fields]) AND ("cognit*"[All Fields]) NOT ("diabetic"[All Fields] OR "diabetes"[All Fields]) AND "humans." Title, abstract, and keywords were carefully examined to identify relevant papers. A parallel search in the ISI Web of Knowledge database was performed to check for additional papers using the same terms. Reference lists of identified manuscripts and reviews were checked manually.

Eligibility criteria

Table 1 shows the PICOS (Participants, Intervention, Comparison, Outcome, Study design) criteria used to define the research question. Studies that fulfilled the following criteria were eligible: study was conducted in

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Description
Population	Healthy adults without psychological disorders or diabetes
Intervention	Glucose, sucrose, fructose, or sugar
Comparison	Placebo
Outcome	Performance in tests of cognition
Study design	Randomized controlled trials or crossover trials

healthy adults; intervention comprised glucose, sucrose, fructose, or sugar and was compared with a matching placebo; [21] study design included only randomized controlled trials or crossover trials; and cognition was reported as an outcome measure. Articles in English, French, Italian, or Spanish were screened. There were no date limits on the publication date, so references identified up until the date of the last search (December 2019) were included. Studies performed in individuals with a psychological disorder or other medical conditions and studies in which glucose or sucrose was coadministered with other substances were excluded. Studies performed in people with diabetes were also excluded to reduce the possible confounding effects of diabetes and its complications.

Selection process and data extraction

Two authors (C.R.G. and J.J.H-M.) independently screened the titles and abstracts of all articles retrieved to identify articles that met the eligibility criteria. The full texts of eligible studies were retrieved and independently assessed by the same researchers. Disagreements were resolved by discussion and consensus. Covidence, a Cochrane technology platform, was used for data management.[22]

Data from all included articles were extracted by one author (J.J.H.M.) and checked by another (C.R.G.). Extracted information included study population, study design, and tools and procedures used to measure cognitive outcomes. Discrepancies were identified and resolved through discussion and consensus.

Quality assessment

Two authors, C.R.G. and J.J.H-M., assessed the quality of included studies twice, using the Cochrane risk of bias tool and the Covidence systematic review software.[22] Conflicts were resolved by discussion. The risk of bias tool rates the following domains: sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Funnel plots were used to evaluate publication bias.

Analysis of cognitive outcomes

A meta-analysis was conducted for outcomes in which at least 2 comparisons were available in a subsample of studies that reported the same outcomes. Studies that reported data for 2 or more intervention groups that differed in the glucose dose administered (eg, 25 g vs 60 g of glucose), age group, or preload condition (eg, fasting, postbreakfast administration, or postlunch administration) were included separately in the meta-analysis. Where a study contributed more than one intervention group but only one control group, the sample size of the control group was divided equally between the interventions.[23] Random-effects models were prespecified a priori, given the heterogeneity across interventions, study populations, and assessment of outcomes. All outcomes are summarized as standardized mean differences (SMDs) with 95%CIs. Statistical heterogeneity was assessed with the I^2 statistic. The strength of evidence was judged according to the precision of the 95%CIs, which allowed relevant differences to be identified and heterogeneity to be assessed. All analyses were stratified by study design (parallel and crossover). All analyses were conducted in Review Manager (RevMan) software, version 5.3 (Cochrane Community).

RESULTS

Search results

Figure 1 shows the PRISMA flow diagram. The initial search yielded 6965 potentially appropriate publications. After removing duplicates and other records that did not meet the eligibility criteria, 593 records were screened by title and abstract, which resulted in the exclusion of 533 records. Full-text review of the remaining 60 papers identified 37 intervention studies that met the inclusion criteria: 34 investigated the effect of glucose on cognition, while 2 investigated the effect of sucrose. In addition, one study assessed the effects of both glucose and sucrose on cognition. Table 2[23–58] provides a detailed overview of studies that addressed the effect of a glucose intervention on cognition, while Table 3[55,59,60] summarizes studies that addressed the effect of sucrose interventions on cognition. Ten of the 35 studies used similar cognitive tests and reported means (± SMDs) for the same outcomes and were included in the meta-analysis. All 10 evaluated the effect of glucose on cognition, while none investigated the effect of sucrose.

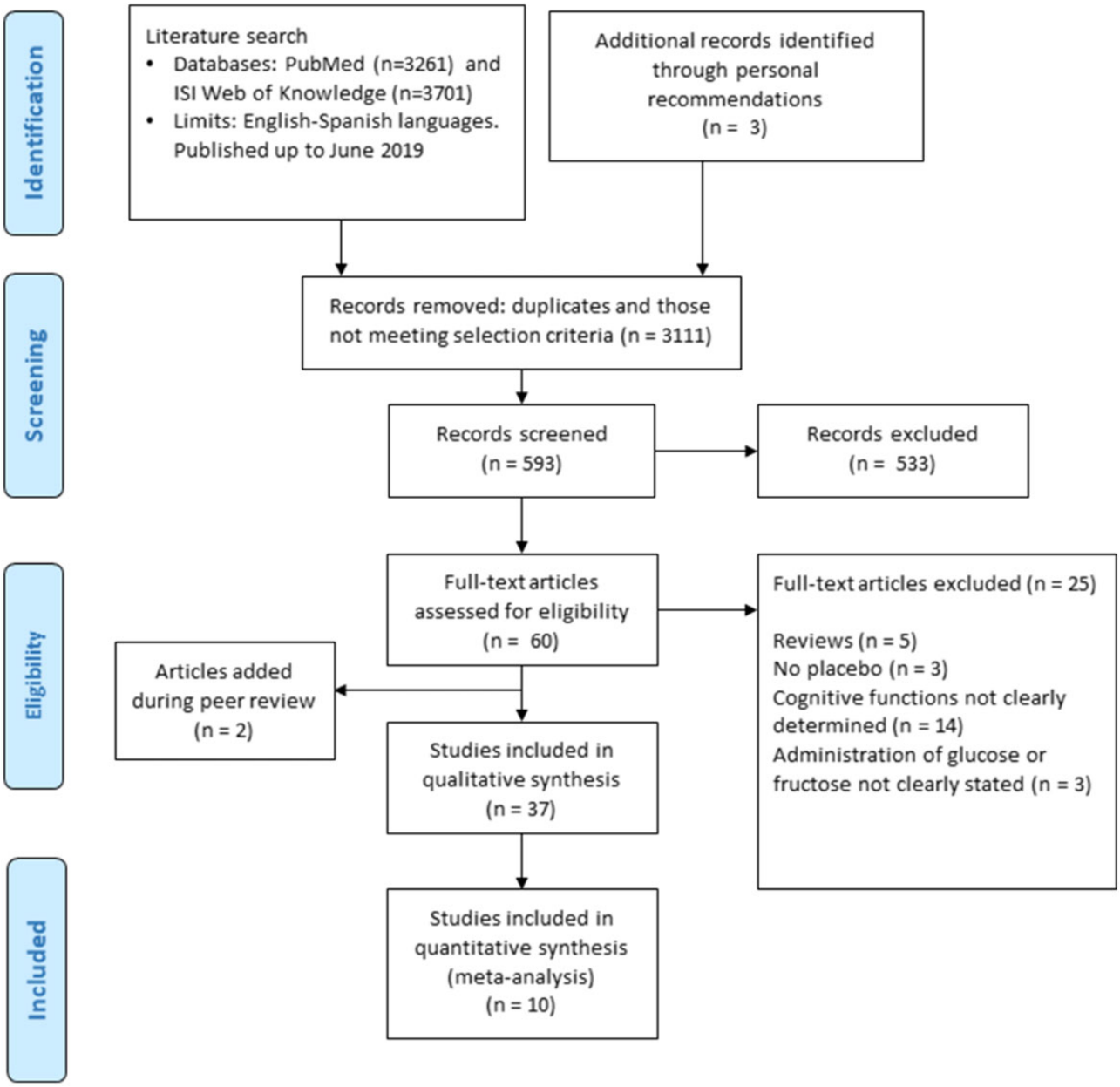

Figure 1 **Flow diagram of the literature search process**

Effect of glucose vs placebo

The 35 studies that examined the effects of glucose drinks on cognition included 1664 participants. Eighteen studies used a crossover or a within-subjects design,[24,25,27,28,33–37,41,43,44,51–54,56,57] and the other 17 used a parallel or a between-subjects design.[23,26,29–32,38–40,42,45–50,55], The main cognitive outcomes were those obtained from the Californian Verbal Learning Test (CVLT), including immediate recall and delayed recall tasks, and the Memory for Digit Span (a subtest of the Weschler Intelligence Scale), and these outcomes were evaluated in the meta-analyses (Figures 2 and 3). For other outcomes, there were major differences and large heterogeneity of cognitive tests employed in some of the studies, and thus other meta-analyses could not be performed (see Table S2 in the Supporting Information online). One study employed a verbal test other than the CVLT[42] and hence was excluded from the meta-analysis.

The 7 studies that focused the immediate recall measure of the CVLT included data on 169 participants in the intervention groups (50 in parallel-design studies and 119 in crossover designs) and 139 in the control groups.[28,29,34,41,43,50,55] Overall, glucose intake was associated with significantly increased cognitive performance (SMD = 0.32; 95%CI, 0.06–0.57; $P = 0.02$). The beneficial effect of glucose was significant only in parallel-design studies (SMD = 0.61; 95%CI, 0.20–1.02;

Table 2 **Overview of studies investigating the effect of glucose compared with placebo on cognition**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
Mantantzis et al (2018)[24]	N=112 (54 young adults, age range 18–27 y; and 58 older adults, age range 65–82 y) Randomized, placebo-controlled, double-blind design	25 g of glucose vs equivalent dose of aspartame	Short-term memory (digit span), processing speed (digit symbol substitution task), and vocabulary knowledge (Mill Hill Vocabulary Scale)	Older adults were faster (t=3.64; P=0.001) and more accurate (t=2.81; P=0.007) in the glucose group. No effect of glucose was found in young adults ($P > 0.50$)
Stollery & Christian (2016)[25]	N=31 (22 F and 9 M). Glucose group: mean age 22.5 y; placebo group: 26.5 y. Randomized, placebo-controlled, crossover trial design	30 g of glucose vs 45 mg of saccharin (placebo)	Object-location binding task	Glucose significantly improved object-location binding (d=1.08) and location memory (d=0.83), but not object memory (d=0.51)
Ullrich et al (2015)[36]	N=17 M (age range 19–40 y; mean age 28.5 ± 4.4 y) Double-blind, balanced, placebo-controlled within-subjects design	Caffeine (200 g) drink + artificially sweetened placebo (sucralose); glucose drink (25 g) + decaffeinated placebo coffee; or decaffeinated placebo coffee + artificially sweetened placebo (placebo condition)	BOMAT (Bochum Matrix Text), logical reasoning; ZVT (Zahlen-Verbindungs-Test), speed of information processing; Digit Span Backward, working memory; False Memory Test, verbal memory; and FAIR-2 (Frankfurt Attention Inventory, revised), attention and the ability to concentrate	No effect of glucose on cognitive performance
Brandt (2015)[47]	N=41 (9 M and 32 F; mean age 19.47 y) Double-blind, placebo-controlled design	Glucose (25 g) drink vs aspartame (5 tablets dissolved in 250 mL of water) drink × 5 (time: T_0 vs T_{15} vs T_{30} vs T_{50} vs T_{70})	PsyScope software for Apple computers. Recognition memory tasks; recollection and familiarity; reaction time; and order effects	No effect of glucose in the inclusion condition (low-effort task conditions), in which recollection and familiarity work in conjunction to support correct recognition. Effects of glucose facilitation were observed in the exclusion condition (difficult task conditions). Errors of commission demonstrated that the glucose group was significantly better at exclusion than the aspartame group [$F_{(1,38)}$=4.48; $P < 0.05$]
Macpherson et al (2015)[53]	N=48 (24 healthy younger adults, mean age 20.6 y, age range 18–23 y; and 24 healthy older adults, average age 72.5 y, age range 65–85 y). Repeated measures, randomized, placebo-controlled, crossover trial design	Glucose (25 g) vs placebo	Recognition memory: single task and dual task	Glucose vs placebo, enhanced recognition memory response time [$F_{(2,46)}$=100.61; $P < 0.001$] and tracking performance in older adults only
Stollery & Christian (2015)[54]	N=80 (54 F and 26 M; age range 18–51 y; mean age 22.4 y) Randomized, allocated to 1 of 6 groups. 3 × 2 placebo-controlled design	First session: 25 g of glucose pre learning, 25 g of glucose post learning, or placebo. Second session (1 wk later): 25 g of glucose or placebo	Paired associates task	In the acquisition phase, there were no differences between those who consumed glucose (18%) and those who consumed placebo (24%) [($F_{1,78}$)=2.3; P=0.178]. In the forgetting phase, glucose intake led to better memory retention (57% vs 44%) [($F_{1,74}$)=6.1; P=0.016]

(continued)

Table 2 **Continued**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
van der Zwaluw et al (2014)[55]	N=43 (older men and women with self-reported memory complaints; age $\geq$ 70 y; mean age 77.7 $\pm$ 5.6 y) Crossover study: three 1-d test trials with 1-wk washout period	Glucose drink (50 g), sucrose drink (100 g), placebo (artificial sweetener)	Rey Auditory Verbal Learning Test; story recall; Paired Associates Learning test; and verbal fluency. Used to measure 4 cognitive domains: episodic memory, working memory, attention and information-processing speed, and executive functioning	Sucrose (100 g) vs placebo: better attention and information processing speed (P=0.04). Sucrose vs glucose: better working memory (P=0.04)
Scholey et al (2014)[56]	N=150 (M and F; age range 18–55 y; mean age 34.8 y) Double-blind, placebo-controlled, randomized, parallel-group study	Glucose drinks (25 g, 60 g, or 60 g + 40 mg of caffeine) vs placebo (sugar-free fizzy orange drink)	Computerized multi-tasking framework, mathematical processing task, Stroop color-word task, memory search task, target tracker	Participants in glucose and placebo groups performed similarly on a task that was very similar to the working memory module in the current study
Owen et al (2013)[57]	N=24 (age range 18–30 y; mean age 20 y) Double-blind, placebo-controlled, randomized, repeated-measures study	25 g and 60 g of glucose vs placebo	Cognitive performance assessed by a selection of computer-controlled tasks: word presentation, immediate word recall, computerized Serial 7's task, computerized Corsi block-tapping task, computerized Serial 3's task, delayed word recall, Bond and Lader visual analogue scales	Glucose improved working memory, with improved performance in the Serial 3's task following 60 g of glucose (P<0.05). 25 g of glucose facilitated performance on the Serial 7's task (P<0.05). Both glucose doses improved spatial working memory (Corsi block task: for 25 g, P<0.05; for 60 g, P<0.01). Verbal declarative memory was also improved (immediate and delayed word recall: both P<0.05). Both glucose doses (25 g and 60 g) improved word recognition reaction time (P<0.05 and P<0.01, respectively)
Scholey et al (2013)[58]	N=20 (11 M; age range 18–35 y) Placebo-controlled, double-blind, crossover	2 [drink: glucose (25 g)/placebo (30 mg of saccharin)] $\times$ 2 (effort: secondary task) design	Remember–Know procedure (cognitive task)	Presence of a secondary task resulted in a global impairment of memory function. Task effort may be a more important determinant of the glucose facilitation of memory effect than hippocampal mediation
Hope et al (2013)[26]	N=12 (6 F; mean age 25.1 $\pm$ 2.1 y). N=24 (21 F; mean age 20.1 $\pm$ 0.7 y) Two linked, double-blind, placebo-controlled design	Glucose (25 g mixed with 100 mL of water and 100 mL of freshly squeezed lemon juice) vs placebo (2 mg of saccharin, 100 mL of water, and 100 mL of freshly squeezed lemon juice)	Eriksen flanker task (complex sensorimotor task) used to assess cognitive control	Higher glucose levels can slow reaction times
Brown & Riby (2013)[27]	N=35 (21 F and 14 M; age range 18–35 y; mean age 22.17 $\pm$ 5.97 y). Randomized, placebo-controlled design	Glucose (25 g) or placebo (37.5 mg of saccharin)	Episodic memory task and Stroop color-naming task	Glucose may facilitate attention as well as verbal episodic memory. The most demanding task conditions are the ones that exhibited glucose sensitivity

(continued)

Table 2 **Continued**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
Jones et al (2012)[28]	N=18 (healthy young adults; mean age 19 y) Blind, placebo-controlled, balanced, randomized crossover study	Drinks containing 40 g of glucose, 16 g of fat, or 40 g of protein vs placebo drink (aspartame)	A tailored version of the Cognitive Drug Research system with the following factors: power of attention, continuity of attention, quality of episodic secondary memory, quality of working memory, quality of memory, and speed of memory	Glucose vs placebo significantly enhanced performance in power of attention [$t_{(48)}$=2.34; $P < 0.05$], particularly 15 min post ingestion [$t_{(48)}$=−3.71; $P < 0.01$]. Performance in attention was worse 60 min post drink ($P < 0.05$). Impaired working memory observed [$t_{(48)}$=2.45; $P < 0.05$]. In quality of memory at 60 min post ingestion, glucose led to significantly impaired memory compared with placebo [$t_{(48)}$=2.52; $P < 0.05$]
Owen et al (2012)[29]	N=30 (age range 18–25 y; mean age 20 y) Double-blind, placebo-controlled, balanced, 6-period crossover study	Drinks containing 0 g, 25 g, or 60 g of glucose after either a 2-h or 12-h fast	Computerized assessment. Cognitive performance, word recall, word recognition, Serial 3's task, Serial 7's task, Corsi block task, Stroop task, Simple Reaction Time task, and Choice Reaction Time task	After a 2-h fast, the 25-g drink resulted in enhanced performance in the demanding working memory task (Serial 7's task) compared with placebo. The 60-g dose increased working memory performance after an overnight fast. Findings suggest that, under conditions of greater glucose depletion, participants might benefit from a higher glucose load
Riby et al[30] (2011)	N=56 (25 M and 31 F). Between-subjects 2 × 2 independent samples design	Placebo (200 mL of water flavored with 5 saccharin tablets and 45 mL of "no added sugar" orange squash); glucose (25 g of glucose dissolved in 200 mL of water flavored with 30 mL of "no added sugar" orange squash)	Prospective memory task and Sustained Attention to Response Task	Neither the main effect of glucose nor the interaction between glucose regulation and treatment was significant ($F_{1,41} = 3.4$; $P = 0.7$)
Adan & Serra-Grabulosa (2010)[31]	N=72 (M and F; age range 18–25 y; mean age 21.07 ± 1.70 y. Double-blind, randomized design	Placebo (150 mL of water); water plus 75 mg of caffeine; water plus 75 g of glucose; or water plus 75 mg of caffeine and 75 g of glucose	Rey Auditory Verbal Learning Test (verbal declarative memory task); Purdue Pegboard Test (fine motor coordination, dexterity, and manipulation speed); Benton Judgment of Line Orientation Test (visuospatial function); California Computerized Assessment Package (reaction time program that measures sustained attention, reaction time, and visual scanning speed); Digit Span of Wechsler Adult Intelligence Scale (general attention and verbal working memory)	Glucose (75 g) vs placebo improved simple reaction time task (P=0.04); Purdue Pegboard Assembly Task ($P < .02$)

(continued)

Table 2 **Continued**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
Gagnon et al (2010)[32]	N=44 (32 F, 12 M; mean age 67.7 y; age range 60–80 y). Between-subjects, double-blind design	Glucose (50 g mixed with 290 mL of water and 10 mL of lemon juice) vs placebo (23.7 mg of saccharin, 290 mL of water, and 10 mL of lemon juice) after 12 h of fasting	Series of attentional measures (neuropsychological tests and computerized dual-task): Trail Making Test, modified Stroop task; computerized dual task	Glucose ingestion appears to momentarily enhance attentional performance in seniors who have fasted for 12 h in tasks requiring switching and dividing attention
Scholey et al (2009)[33]	N=120 (healthy; 77 F and 43 M; mean age 21.6 y) Double-blind, randomized, parallel-group study	Glucose (25 g) drink or placebo (30 mg of saccharin)	Word recognition and tracking tasks. Word presentation and program design	Compared with placebo, the glucose drink significantly improved tracking performance during encoding, but not memory
Smith & Foster (2008)[34]	N=32 (12 M and 20 F; age range 14–17 y; mean age 15.6±0.9 y). Within-subjects design, ie, a single within-subjects factor (treatment), with 2 levels (glucose, placebo). A subsequent mixed-model design also incorporated a single between-subjects factor (treatment order), with 2 levels (glucose first, placebo first)	25 g of glucose dissolved in 300 mL of water vs placebo [5 Equal tablets (10% aspartame) dissolved in 300 mL of water]	Verbal episodic memory performance with Modified California Verbal Learning Test-II and Bond–Lader scales	Findings suggest that the glucose memory facilitation effect, previously observed in adults, can be extended to adolescents
Riby et al (2008)[35]	N=33 (19 F; age range 35–55 y) Counterbalanced order	Placebo (200 mL of water flavored with 5 saccharin tablets and 45 mL of "no added sugar" whole orange squash) vs same ingredients plus 25 g of glucose vs same ingredients plus 50 g of glucose	National Adult Reading Test (verbal intelligence quotient), digit symbols (speed of cognitive processing), letter cancellation test (attention), Trail-Making tasks, digit span forward and backward (short-term memory), and category fluency (semantic memory retrieval)	Episodic memory improved after glucose ingestion when task demands were high. Blood glucose concentration also predicted performance across a number of cognitive domains
Riby et al (2006)[37]	N=13 older adults (mean age 68 ± 5.9 y) and 14 younger adults (mean age 30.1±4.6 y). Repeated measures, counterbalanced, double-blind design	25 g of glucose vs 38 mg of saccharin	Battery of episodic (eg, paired associates learning) and semantic memory (eg, category verification) tasks under low and high cognitive loads	Glucose appeared to aid episodic memory. Cognitive load did not exaggerate the facilitative effect. There was little evidence to suggest that glucose can boost semantic memory retrieval, even when the load was manipulated. One exception was that glucose facilitated performance during the difficult verbal fluency task
Meikle et al (2004)[38]	N=25 (17 F and 8 M; age range 18–52 y; mean age 28.4 ± 9.3 y). Participants were divided into a younger group (n=14; mean age 21.8±3.3 y) and a middle-aged group (n=11; mean age 38.4±6.7 y). Repeated measures, counterbalanced, double-blind design	25 g vs 50 g glucose vs placebo	Battery of memory and nonmemory tasks was administered; including tests of episodic and semantic memory, attention, and visuospatial functioning	Glucose ingestion largely facilitated performance on tasks with a memory component. Notably, task demands and age (young vs middle-aged) contributed to the magnitude of memory enhancement. This suggests an age- and load-specific benefit of glucose intake

(continued)

Table 2 **Continued**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
Scholey & Fowles (2002)[39]	N=45 (35 F and 10 M; mean age 22.58±6.50 y). Randomized placebo controlled trial	Placebo (water and 2.9 g of saccharin) or glucose (water and 25 g of glucose)	Kinesthetic memory (maze test) and Profile of Mood States	In maze performance, the placebo group scored significantly lower than the glucose group [$t_{(2,42)}$=2.744; $P < 0.01$)]
Flint & Turek (2003)[40]	N=67 (15 M and 52 F; mean age 19.49±4.35 y). Double-blind, randomized design	Glucose (10 mg/kg, 100 mg/kg, and 500 mg/kg, or 50 g) or placebo (23.7 mg of saccharin)	TOVA (Test of Variables of Attention), a continuous performance test.	100 mg/kg glucose group performed worse on measures of commission errors, postcommission responses, and postcommission response time variability ($P < 0.05$). Large doses of glucose that increase blood glucose levels do not influence attention, but a moderate dose (100 mg/kg) selectively impairs measures of impulsivity or disinhibition
Sünram-Lea et al (2002)[41]	N=60 (26 M and 34 F; age range 19–26 y; mean age 21 y). Placebo-controlled, double-blind study. 2 × 3 design (glucose, aspartame) on memory performance under different conditions of glucose administration (immediate anterograde, delayed anterograde, immediate retrograde)	Glucose (25 g) vs placebo (aspartame)	Modified California Verbal Learning Test: evaluated immediate , short-delay, and long-delay long-term memory (free recall, cued recall, recognition) from a supraspan word list. Rey-Osterrieth Complex Figure test: evaluated long-term memory for nonverbal materials. Forward/backward digit span: evaluated working memory span	Results showed that both pre- and postacquisition oral glucose administration (25 g) can improve memory performance. Glucose enhances memory, even when given after learning, and this effect is observed at least up to 24 h after glucose administration
Scholey et al (2001)[42]	N=20 (11 M and 9 F; mean age 22.7 y; age range 20–30 y). Placebo-controlled, double-blind, balanced, crossover study	25 g of glucose powder in 250 mL of water and 25 mL of no-added-sugar apple and blackcurrant squash vs a placebo drink that was similar but with 30 mg of saccharin substituted for glucose	Serial subtraction task (computerized Serial 7's), a somatically matched control task (key-pressing), a short-interval word memory task, and a word retrieval task (verbal fluency)	Glucose consumption significantly improved performance on Serial 7's task, with a trend toward improved performance on word retrieval and no effect on the word memory task
Sünram-Lea et al (2001)[43]	N=60 (mean age 21 y; age range 18–28 y). 2 × 3 design (fasting, breakfast, lunch). Fasting intervals (2-h fast vs overnight fast), fasting times (morning vs afternoon), and fasting glycemic conditions by double blind procedure	Glucose (25 g) vs aspartame (5 tablets) in 300 mL of water	Measures of verbal and nonverbal memory were used. Modified California Verbal Learning Test: evaluated immediate, short-delay, and long-delay long-term memory (free recall, cued recall, recognition) for a supraspan word list. Rey-Osterrieth Complex Figure test: evaluated long-term memory for nonverbal materials. Forward/backward digit span: evaluated working memory span	Significant glucose facilitation effect on long-term verbal memory performance was observed. In addition, glucose significantly enhanced long-term spatial memory performance. Glucose produced an essentially equivalent effect, whether given after an overnight fast or after a 2-h fast following breakfast or lunch. There was no effect of drink or time of day on working memory performance

(continued)

Table 2 **Continued**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
Green et al (2001)[44]	N=26 (healthy individuals; age range 18–40 y) Crossover study: 5 test sessions	Glucose (50 g) drink or placebo drink (aspartame)	6-min visual analogue of the Bakan vigilance task; an immediate verbal free-recall task; an immediate verbal recognition memory task; and a measure of motor speed (2-finger tapping)	Glucose administration improved recognition memory times, in direct contrast to previous findings in the literature. Glucose administration also improved performance on the Bakan task (relative to the control drink), but only in sessions in which participants were told they would receive glucose and not when they were told they would receive aspartame
Kennedy & Scholey (2000)[45]	N=20 (6 M and 14 F; mean age 20.4 y; age range 19–30 y). Placebo-controlled, double-blind, balanced, crossover study	25 g of glucose powder dissolved in 250 mL of water and 25 ml of Robinson's Low-Calorie Orange Squash. Placebo was 30 mg of saccharin dissolved in 250 mL of water and 25 mL of Robinson's Low-Calorie Orange Squash	Two serial subtraction tasks (Serial 3's and Serial 7's) and a word retrieval (verbal fluency) task. Serial 7's task was rated as the most mentally demanding task, followed by word retrieval task, then Serial 3's task	Glucose consumption significantly improved performance on Serial 7's task [$F_{(1,18)}$=8.99; P <0.01]
Metzger (2000)[46]	N=34 (23 F and 11 M; mean age 21.1 y; age range 17–45 y). Blind design	Lemonade sweetened (224 g) with either glucose (50 g) or saccharin (23.7 mg)	Facial recognition task in young adults	Glucose enhanced performance in facial recognition task in healthy young adults. Fewer false alarms (U = 85.5; P<0.05) and marginally higher d scores (U = 97.5, 0.05; P<0.10)
Martin & Benton (1999)[48]	N=80 (mean age 22.6 y). Four-way analysis of variance: glucose drink vs placebo × breakfast/no breakfast × blocks (1– 4/5–8) × distracter interval (3 s, 6 s, 9 s, 12 s, or 18 s), with the last 2 factors as repeated measures	Glucose drink (50 g of glucose dissolved in 250 mL of water and 2 tbsp of sugar-free Robinson's Whole Orange Squash; 2 tsp of lemon juice were added to decrease sweetness) vs placebo (same ingredients, with the exception of the glucose powder and the addition of 2 g of Sweetex, a low-calorie sweetener that contains aspartame and saccharin)	Brown–Petersen task (a test of memory)	Those who had not eaten breakfast but had received a placebo drink recalled the trigrams to a lesser extent than those in the other 3 groups. Thus, a drink containing glucose nullified the negative consequences of not eating breakfast. In those who had eaten breakfast, an additional glucose drink was of no further benefit
Donohoe & Benton (1999)[49]	N=67 F (mean age 21.8 ± 5.1 y). Double-blind study	Glucose: 50 g of glucose powder dissolved in a mixture of 250 mL of water and 2 tbsp of Robinson's Whole Orange Squash (sugar-free); 2 tsp of lemon juice were added to make the drinks less sweet. Placebo drinks contained the same ingredients, with the exception of the glucose powder, which was replaced with 3 g of Sweetex, a low-calorie sweetener containing aspartame and saccharin	Logical reasoning, Embedded Figures Test, water jars task, verbal fluency, Porteus Maze, and Block Design task	Type of drink consumed did not influence time required to solve the water jars task [$F_{(1,65)}$=0.09, NS] or a logical reasoning test [$F_{(1,65)}$=2.09; NS] and did not affect Embedded Figures scores [$F_{(1,52)}$=1.89; NS]. Consumption of a glucose-containing drink resulted in faster performance on the Porteus Maze and greater verbal fluency

(continued)

Table 2 **Continued**

Reference	Population characteristics and study design	Intervention	Cognition aspects measured and/or tests used	Results
Foster et al (1998)[50]	N=30 F (age range 18–22 y; mean age 19.5 y). Experiment followed a between-participants design, with 10 participants per treatment group	Glucose (25 g in 300 mL of water); saccharin (37.5 mg in 300 mL of water (sweetness matched to a dose of glucose); or water (300 mL)	Modified California Verbal Learning Test: evaluated immediate, short-delay, and long-delay long-term memory (free recall, cued recall, recognition) for a supraspan word list. Rey-Osterrieth Complex Figure test: evaluated long-term memory for nonverbal materials. Forward/backward digit span: evaluated working memory span	25 g of glucose enhanced memory performance on a long-term verbal memory recall task but had no significant benefits on measures of digit span or spatial memory
Messier et al (1998)[51]	N=100 F (age range 17–48 y; mean age 21.3 ± 4.6 y; median age 20.0 y)	Eight groups: water, saccharin, or 1 of 6 doses of glucose. Tap water (230 mL); a saccharin solution (222.7 mg of saccharin and 3 g of unsweetened, grape Kool-Aid powder dissolved in 1 L of water); or glucose (220.1 g of glucose, 17.6 mg of saccharin, and 3 g of unsweetened, grape Kool-Aid dissolved in water was adjusted to provide a dose of 10 mg, 100 mg, 300 mg, 500 mg, 800 mg, or 1000 mg of glucose per kilogram of body weight)	List of 10 words and 8 experimental lists of 20 items. The frequency of use in print, the subjective frequency, and the imagery-evoking value of the 8 experimental lists were controlled in the selection of items	Glucose enhanced the primacy effect as defined by recall of the first 5 items of the lists
Hall et al (1989)[52]	N=23 (11 elderly volunteers; age range 58–77 y; mean age 67.4 y; and 12 young participants; age range 18–23 y; mean age 20 y). Counter-balanced, crossover design	Placebo (473 mL of lemon-flavored beverage sweetened with sodium saccharin (23.7 mg) or glucose (50 g)	Wechsler Memory Scale	(1) Glucose enhanced memory in elderly and, to a lesser extent, in young participants; and (2) glucose tolerance in individual participants predicted memory in elderly but not in young participants on both glucose and saccharin test days

Abbreviations: NS, not significant; tbsp, tablespoon; tsp, teaspoon.

Table 3 **Overview of studies investigating the effect of sucrose compared with placebo on cognition**

Reference	Population characteristics and study design	Intervention	Cognition measure	Results
van der Zwaluw et al (2014)[55]	N=43 (older men and women with self-reported memory complaints; age $\geq$ 70 y; mean age 77.7 $\pm$ 5.6 y. Crossover study: three 1-d test trials with 1-wk washout period	Glucose drink (50 g), sucrose drink (100 g), placebo (artificial sweetener)	Rey Auditory Verbal Learning Test; story recall; Paired Associates Learning test; and verbal fluency. Used to measure 4 cognitive domains: episodic memory, working memory, attention and information-processing speed, and executive functioning	Sucrose (100 g) vs placebo: improved attention and information-processing speed ($P = 0.04$). Sucrose vs glucose: improved working memory ($P = 0.04$)
Taljaard et al (2013)[59]	N=398 children (age range 6–11 y) Double-blind, randomized, controlled intervention study	Four different formulations of the beverages: (1) micronutrients with sugar; (2) no micronutrients (control beverage) with sugar; (3) micronutrients with a nonnutritive sweetener; and (4) no micronutrients (control beverage) with a nonnutritive sweetener	Kaufman Assessment Battery for Children Second Edition subtests and the Hopkins Verbal Learning Test	Sugar had beneficial effects on cognitive test scores
Wolraich et al (1994)[60]	N=48 (25 preschool children with normal glucose sensitivity; mean age 4.7 y; age range 3–5 y; and 23 school-aged children thought to respond adversely to sugar; mean age 8.1 y; age range 6–10 y) Double-blind controlled trial	Children and their families followed a different diet for each of 3 consecutive 3-wk periods. One diet was high in sucrose with no artificial sweeteners, another was low in sucrose and contained aspartame as a sweetener, and the third was low in sucrose and contained saccharin (placebo) as a sweetener	Cognitive performance	In the normal preschool group, ratings on the cognition subscale of the Pediatric Behavior Scale were significantly better during the sucrose diet than during the aspartame and saccharin diets ($P < 0.008$). Neither sucrose nor aspartame produced discernible cognitive or behavioral effects in normal preschool children or in school-aged children believed to be sensitive to sugar

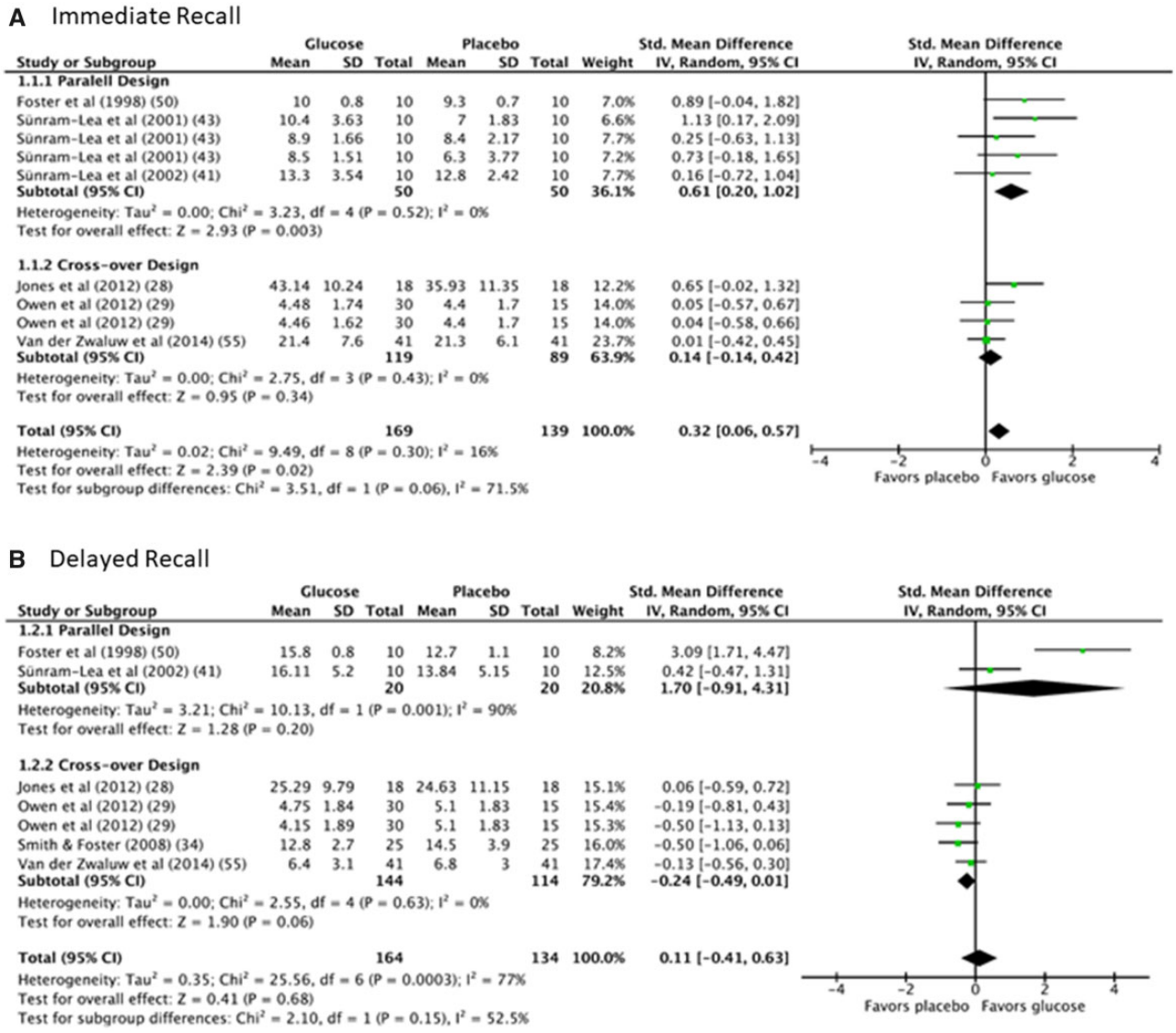

Figure 2 **Random-effects meta-analysis of standard mean differences (SMDs) and 95%CIs for studies that included data obtained with the California Verbal Learning Test.** Meta-analysis categories included (A) the immediate recall task and (B) the delayed recall task of the test. Pooled summary data for each task represent the SMD and 95%CI. The size of the data markers indicates the weight assigned to each study in the meta-analysis. Squares represent the SMD, bars represent the 95%CI, and diamonds represent the pooled analysis

$P = 0.003$) and not in crossover studies (SMD = 0.14; 95%CI, −0.14 to 0.42; $P = 0.34$). The effect of glucose on the CVLT delayed recall task was null (SMD = 0.11; 95%CI, −0.41 to 0.63; $P = 0.68$) (Figure 2). Similarly, the effect of glucose on the digit span task was not significantly different from that of the control (SMD = 0.11; 95%CI, −0.15 to 0.38; $P = 0.40$) (Figure 3).

The remaining studies not included in the meta-analysis reported diverse positive effects of glucose on the performance of several cognitive tasks. For example, significant improvements in response to a glucose load were observed in the following cognitive assessments: object-location task,[25] hippocampal function (process dissociation procedure),[47] memory response time,[53] attention and information-processing speed, spatial working memory,[57] reaction time,[26] verbal memory,[31] attentional performance,[32] tracking performance,[33] episodic memory,[27,37] general memory performance,[38] recognition memory time,[44] serial subtraction task,[45] facial recognition task,[46] Porteus Maze Test,[49] recall of word lists,[51] kinesthetic memory,[39] and scores on the Wechsler Memory Scale.[52]

However, 6 other studies found no significant effect of glucose compared with placebo on different memory tasks, including object memory, [25] working memory, [56]

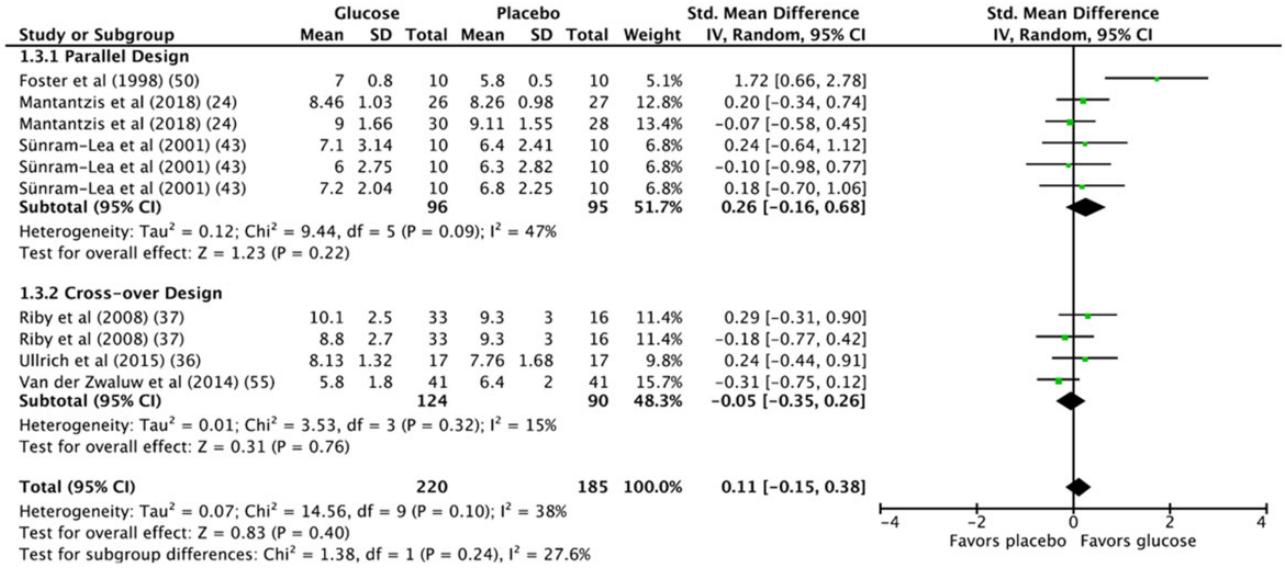

Figure 3 **Random-effects meta-analysis of standard mean differences (SMDs) and 95%CIs for studies that included data obtained with the digit span test**. Pooled summary data for the task represent the SMD and 95%CI. The size of the data markers indicates the weight assigned to each study in the meta-analysis. Squares represent the SMD, bars represent the 95%CI, and diamonds represent the pooled analysis

attention tasks,[40] relational memory,[54] prospective memory,[30] and word memory.[42]

On the other hand, the study of Scholey et al[58] showed an overall impairment in memory function after a 25-g dose of glucose compared with placebo, and Flint and Turek[40] also described impaired impulsivity control after glucose intake. In a study of healthy adults, Jones et al[28] observed enhanced attention 15 minutes after glucose ingestion, but attention and working memory were worse after 60 minutes.

Effect of sucrose vs placebo

Three studies (n = 489 participants in total) used sucrose drinks as the intervention. In a crossover study performed in 43 elderly participants, the sucrose drink improved the cognitive domains of attention and information-processing speed when compared with placebo.[55] This study was also included with the glucose studies because a glucose drink was also used in a separate arm. Interestingly, the individuals in the glucose drink group showed better working memory than those in the sucrose drink group.

In an 8.5 month follow-up study conducted in 398 children aged 6 to 11 years, 4 different formulations were evaluated: micronutrients with sugar; no micronutrients with sugar; micronutrients with a nonnutritive sweetener; and a control without micronutrients or a nonnutritive sweetener.[59] The results showed that sucrose plus micronutrients, compared with micronutrients alone, had beneficial effects on cognitive test scores in the Kaufman Assessment Battery for Children Second Edition subtests and the Hopkins Verbal Learning Test.[59] Wolraich et al[60] compared the effects of different types of diets in children: high in sucrose with no artificial sweeteners; low in sucrose with aspartame; and low in sucrose with saccharin. They found no significantly positive effects of sucrose on cognitive or behavioral tasks compared with the artificial sweeteners.

Heterogeneity of the reported outcomes

In the meta-analysis of immediate recall outcomes, overall heterogeneity was very low ($I^2 = 16\%$), both in the group of studies with a parallel design (χ^2=3.23; $P = 0.52$; I^2=0%) and in the group with a crossover design (χ^2=2.75; $P = 0.30$; I^2=0%). In contrast, heterogeneity for the delayed recall analysis was higher (I^2=77%), and study design significantly influenced the overall direction of the association, with parallel-design studies showing significant heterogeneity (χ^2=10.13; $P = 0.001$; I^2=90%) compared with crossover studies (χ^2=2.55; $P = 0.63$; I^2=0%). In the meta-analysis of studies analyzing the digit span test, the global heterogeneity was low (I^2=38%), and study design significantly affected the heterogeneity, with parallel-design studies being more heterogeneous (χ^2=7.62; $P = 0.05$; I^2=47%) than crossover studies (χ^2=3.53; $P = 0.32$; I^2=15%).

Risk of bias

More than half of the studies were at high risk of bias for sequence generation, and about half were at high

risk of bias for allocation concealment (see Figure S1 in the Supporting Information online). This was mainly due to the lack of description of the randomization process or to unclear adherence to the trial guideline [eg, CONSORT (Consolidated Standards of Reporting of Trials) guidelines].[61] About 30% of studies were at high risk of bias for the blinding of outcome assessors. The item with the lowest risk of bias was incomplete outcome data. Funnel plots were computed for each outcome, but there were very few studies to detect and formally test for asymmetry[23] (see Figure S1 in the Supporting Information online).

DISCUSSION

Only limited evidence of the effects of glucose or sucrose intake on cognition was found in this systematic review and meta-analysis, with some evidence favoring glucose when individuals performed immediate verbal tasks and no evidence to suggest that glucose intake impairs cognitive performance.

Strengths of this study include the rigorous methodology to objectively evaluate the effect of glucose and sucrose on cognition and the choice of randomized study designs. The major limitation is related to the use of a very diverse battery of tests in most studies, hence the small number of studies that were combined in the meta-analysis and the limited power to examine the effect of glucose on cognition. A number of study characteristics need to be considered to evaluate the effect of glucose administration on brain function, including study design, dose of glucose administered, types of cognitive tasks used, age of participants, sensitivity of peripheral organs to glucose, and time between glucose load intervention and cognitive assessment. The selection of the cognitive outcome may have been the most limiting factor for evaluating the effect of glucose on cognition. Most studies examined memory, instead of other cognitive functions such as executive functions and other higher functions. Although the protocol for the present review initially included the evaluation of these functions, the lack of studies limited the results. Furthermore, the wide variability in the cognitive assessments employed in the different studies did not allow a more significant meta-analysis to be performed. Only verbal learning (immediate recall and delayed recall) and digit span tasks were used in at least 2 studies, and therefore only these outcomes were meta-analyzed.

The studies included in this meta-analysis suggest that glucose facilitates performance on verbal declarative memory when evaluated by immediate and delayed recall tests (although high heterogeneity was observed in the latter). Glucose also seems to improve recognition speed, spatial and numerical memory, and episodic memory, for example, in those tasks with high cognitive demands.[35,37,45,47] Considering that these tasks may demand a higher glucose supply, which is regulated by insulin availability in the brain,[62] it has been proposed that the positive effect of glucose on cognition may be a secondary consequence of elevated plasma insulin levels, rather than a rise in blood glucose.[41] In fact, Smith and Foster[34] proposed that individuals who showed a memory enhancement effect were characterized by better glucose regulation. In addition, this elevation of insulin may boost glucose utilization in the hippocampus, which may result in improved memory.[63] Nevertheless, it is important to note that the effect was only significant in studies with a parallel design. Crossover designs are more efficient than parallel designs, since they can be conducted with a smaller sample size; on the other hand, this makes them more susceptible to losses during follow-up. In addition, there are 2 effects that must be controlled to avoid bias in crossover studies. The first is the period effect, which refers to changes a participant may experience between the first and the second periods of the study. The second is the carryover effect, which refers to a possible effect of the previous intervention on the subsequent one.[64] Therefore, it is plausible that lack of significance in the results observed in the present meta-analysis may be attributable to these effects. Future studies may elucidate the facilitation effect of glucose in different brain regions, which could explain why glucose seems to improve some cognitive functions, but not others.

Sucrose intervention studies provided only a limited amount of data, but none of them found a negative effect on cognition. The trial with the largest population was funded by a prominent beverage company.[59] The authors found cognitive benefits in children, but the follow-up period was 8.5 months, so any comparison with shorter-term studies should be done with caution. In another study in children, no alteration of cognitive processes was observed,[60] but this study was carried out in 1994, so certain methodological differences compared with more recent studies cannot be ruled out.[60] The other study with sucrose found improvements in working memory in elderly participants,[55] as previously described with glucose.[25] There were no sucrose interventions in young adults. Therefore, the lack of studies that used sucrose makes it difficult to make comparisons between glucose and sucrose with regard to effects on cognition.

An interaction between age and the effect of glucose on cognition has also been suggested, especially with regard to facial recognition tasks,[46] although there are no systematic reviews supporting these observations. For example, the enhancement effect of glucose

was more evident in young adults than in middle-aged adults.[38,52] Flint and Turek[40] suggested that glucose may have an effect only among young adults, most likely by improving impulsivity control and reducing disinhibition. However, glucose administration may also increase attention performance in older adults after a fasting period.[32] In addition, Mantantzis et al[24] recently described improved cognitive performance after a glucose intervention, but only among older adults and not in young adults.

With regard to the dose effect, Jones et al[28] observed that the benefits of glucose on attention performance were evident only with a 40-g dose and only 15 minutes after administration. Other authors have reported that lower doses (25 g) are enough to increase cognitive performance,[24,25,53] while still others have described no effect at such doses.[47] On the other hand, Hope et al[26] concluded that higher glucose levels can even reduce cognitive control and slow reaction times in sensorimotor processing tasks.

This apparent paradoxical effect of glucose on brain functions may be related to other dietary characteristics of the trial participants, especially macronutrient intakes. Reichelt[6] has reported that the consumption of high-fat and high-sugar diets has a particularly negative impact on cognition when consumed during adolescence, suggesting that brain performance may be modulated by dietary patterns during adolescence.[65,66] Other factors, such as clinical status or the presence of chronic disease or psychological disorders, can also affect brain function. However, studies performed in patients with diabetes or in individuals with psychological disorders were excluded from this present review. Those disorders that affect blood glucose levels can influence cognitive performance, and the results may not translate to healthy individuals.

CONCLUSION

The results derived from the present review suggest that glucose has a moderately beneficial effect on cognition, especially on recognition memory and attention processes. The meta-analysis shows that the effect was significant for immediate recall tasks in verbal memory assessments, which also showed lower heterogeneity. The number of studies investigating the effect of sucrose on cognition is too small to allow any meaningful conclusion. In addition, the disparities in cognitive tasks, population characteristics, and doses of glucose investigated limit the interpretation of the data reviewed here. High-quality trials using standardized cognitive measurements are needed, since the studies performed to date do not constitute a robust body of evidence to firmly establish the effect of glucose or sucrose on cognition.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **PRISMA 2009 checklist.**

Table S2 **Measures of cognitive performance used in the studies included in the present systematic review.**

Figure S1 **Results of assessment for (A) risk of bias and (B) risk of publication bias.**

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