Etiology and Pathophysiology

Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis

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Summary

High adiposity in middle age is associated with higher dementia risk. The association between weight loss and cognitive function in older adults is still controversial. A meta-analysis was undertaken to estimate the effectiveness of intentional weight loss on cognitive function in overweight and obese adults. A structured strategy was used to search randomized and non-randomized studies reporting the effect of intentional and significant weight loss on cognitive function in overweight and obese subjects. Information on study design, age, nutritional status, weight-loss strategy, weight lost and cognitive testing was extracted. A random-effect meta-analysis was conducted to obtain summary effect estimates for memory and attention–executive domains. Twelve studies met inclusion criteria. Seven were randomized trials and the remaining five included a control group. A low-order significant effect was found for an improvement in cognitive performance with weight loss in memory (effect size 0.13, 95% CI 0.00–0.26, $P = 0.04$) and attention/executive functioning (effect size 0.14, 95% CI 0.01–0.27, $P < 0.001$). Studies were heterogeneous in study design, sample selection, weight-loss intervention and assessment of cognitive function. Weight loss appears to be associated with low-order improvements in executive/attention functioning and memory in obese but not in overweight individuals.

Introduction

Obesity is associated with increased cardiovascular and metabolic risk (1). Obesity in middle age and its associated cardiovascular risk have also been linked to lower brain volume (2) and increased risk of dementia and Alzheimer's disease (3,4), and the link between high adiposity and worse cognitive outcomes is biologically plausible, although the evidence remains inconsistent (5,6). Higher body mass index (BMI) has been associated with brain

We followed the PRISMA checklist and endeavoured to provide all the relevant information.

volume deficits in frontal, temporal, parietal and occipital lobes, with the atrophic pattern being consistent in two independent older-aged populations (7).

Weight loss is the primary treatment strategy for obesity. Modest weight loss (5–10%), and moderate rates of weight loss (0.5 kg week^{-1}) are associated with changes in metabolic flexibility and vascular reactivity and reduction of the risk for cardiovascular and metabolic diseases (8–13). These changes are primarily related to the positive effects on intermediate metabolism, endothelial function, autonomic regulation, inflammation and oxidative stress (14–17). Changes in dietary patterns associated with weight-loss treatments may also improve

cognition. Dietary manipulations have been found to affect cognitive function depending on their energy content and macronutrient composition (18–21). Both positive and negative effects have been identified. For example, glucose supplementation has been found to improve cognitive performance in young adults (22), whereas short-term fasting was found to be detrimental in children (23) but not in young adults (24). However, whether intentional weight loss and its long-term maintenance in overweight/obese individuals can positively influence cognitive performance and modify dementia risk remains unanswered.

Weight-loss improvements in vascular (e.g. hypertension, pro-thrombotic state) and metabolic (e.g. insulin resistance, inflammation, hyperuricaemia, dyslipidaemia) risk factors (25) in overweight and obese individuals may have secondary influences on cognition. This putative association may be particularly important in the older-aged population because the prevalence of both obesity (26) and dementia (27) is increasing and the evidence that they may be mechanistically linked is emerging (28). Weight loss induced by a 25% caloric restriction in overweight subjects was associated with changes in metabolic and vascular functions mediated by improvements in whole-body metabolic efficiency and biomarkers of longevity (29–32).

Here, we review evidence from randomized and non-randomized studies which have investigated the efficacy of intentional and significant weight loss on cognitive function in overweight and obese subjects. If clinically meaningful weight loss may positively impact on metabolic and vascular functions and this could have important implications for improving cognition in overweight and obese individuals at risk of cognitive decline and dementia.

Methods

Search strategy

The meta-analysis was conducted according to PRISMA guidelines (33). References were identified through searches of EMBASE, MEDLINE and PsycINFO (1966 to May 2010) using terms related to weight loss and cognitive domains (e.g. 'weight loss', 'exercise', 'drug' 'caloric restriction', 'diet', 'cognition', 'memory', 'executive', 'attention'), for titles and abstracts and limiting the search to articles on humans published in English. Reference lists of included papers and relevant reviews were searched for articles potentially missed during the electronic search. The first screening phase was based on analysis of titles and abstracts, conducted independently by authors B. S. and M. S. using an identical review protocol. When full agreement had been reached, the article was either discarded or moved to the next phase. In case of disagreement, the article was moved to the next phase to increase the inclusiveness level. In the second phase, the full text was

retrieved and assessed for a final decision applying a standardized approach consistent with the inclusion and exclusion criteria stated below. Kappa statistics were calculated to measure level of overall agreement. Data were incompletely reported in three included studies and the corresponding author was contacted to obtain the raw data to conduct the meta-analysis.

Study selection

Studies were included if they were conducted on adult overweight or obese subjects and met the following criteria (i) statistically significant and intentional weight loss greater than 2 kg which was considered as clinically meaningful and likely to be associated with improvements in metabolic and vascular functions; and (ii) reported assessment of cognitive function before and after weight loss in any domain using a standardized and validated neuropsychological measure. Any weight-loss interventions (randomized and non-randomized, controlled and non-controlled) were included. Exclusion criteria included (i) dementia diagnosis without objective neuropsychological assessment; (ii) non-intentional significant weight loss (weight loss post diagnosis of dementia or disease-related weight loss); (iii) weight loss related to extreme conditions (combat training, dehydration during surgery or extreme environmental conditions); and (iv) dietary interventions having as objective the investigation of the effects of changes in macronutrient composition on cognitive functions and not associated with a significant decrease in body weight.

Only studies where significant weight loss occurred were included in order to link cognitive function to clinically meaningful weight changes. A significant weight loss of at least 2 kg would be expected to have an impact on metabolic and cardiovascular health (34–38) and potentially influence cognitive function. Furthermore, a weight reduction of 0.5 kg week^{-1} of a weight-loss intervention is considered as clinically acceptable for evaluating the effectiveness of that intervention (39,40) and a weight loss of at least 2 kg after 4 weeks is considered as the clinical target to evaluate the effectiveness of obesity pharmacological treatments (41).

Data quality was based on the adequate description of the study characteristics (age, baseline BMI), inclusion of patients representative of the overweight and obese population likely to benefit from weight loss, description of weight-loss strategy including duration and nutritional characteristics (macronutrient composition and/or energy content), indication of the amount of weight lost (absolute or proportional) and level of statistical significance, use of standardized, validated neuropsychological tests for the assessment of cognitive function and sufficient description of the modality of administration of each cognitive test including strategies to minimize practice effects.

Data extraction

The information from all relevant studies was gathered by two authors (B. S. and M. S.) using a standardized form. Data extracted included: information on author, location, study duration, study design (number of groups, parallel or cross over, control group, randomization), sample size, gender, baseline BMI, age, number of completers, nutritional characteristics of the intervention (macronutrient composition, dietary energy content or proportion of caloric restriction relative to baseline energy requirements), cognitive test, amount of weight loss (absolute or relative to baseline) and effects of weight loss on cognitive function.

Data analysis

A meta-analysis was conducted using Comprehensive Meta-Analysis software (Biostat, Engelwood, NJ, USA). Both random- and fixed-effects models were computed. Data are presented as standardized mean differences (SMD, Cohen d) of the treatment effect on cognitive domains, standard error and 95% confidence intervals of the SMD. The Forest Plot was used to summarize graphically the pooled effect size derived from the analyses of the memory and attention–executive domains. Statistical heterogeneity across studies was assessed using the I^2 test. The random-effect model was used for pooling results if significant statistical heterogeneity was present to provide a more conservative estimate of the treatment effect. Funnel plots were used to evaluate publication bias and selective reporting bias.

Neuropsychological tests were divided according to cognitive domain (memory, attention, executive and attention/executive). Effects were analysed for the domain of memory and a combined measure of attention–executive function. Memory scores for each weight-loss intervention in each study were entered individually in the meta-analysis. Attention/executive function scores for each weight-loss intervention in each study were averaged to facilitate the analysis in consideration of the large number of groups and cognitive tests potentially being entered. The direction of the effect (improvement or decline) on cognitive function was taken into consideration. Only baseline and final, post-weight loss cognitive measurements were included. The main analysis evaluated the effect of weight loss on cognition relative to baseline values. Baseline and post-weight loss cognitive scores (mean, SD, n) were entered into the model and an imputed pre–post correlation (r) value of 0.50 was selected based on the assumption that this correlation value would minimize the error of the estimates with the assumption that pooled and paired variances are the same. A sensitivity analysis was conducted to test the validity of the models. Changes in effect size were evaluated in each model after entering a sequential range of correlation values ($r = 0.10$, $r = 0.25$, $r = 0.50$, $r = 0.75$, $r = 0.90$) (Tables S6

and S7). Additional analyses were conducted to assess changes in effect size with baseline BMI. We stratified the analyses for both memory and attention/executive function using BMI categories including overweight (BMI = 25–29.9 kg m^{-2}) and obese (BMI $\geq$ 30 kg m^{-2}). The effect size (random model) was reported for both BMI groups and both cognitive domains. In addition, the effect size was calculated after the exclusion of the studies including a physical activity intervention as part of the weight-loss strategy (42,43) as well as of the study investigating the effects of bariatric surgery on cognitive function (44).
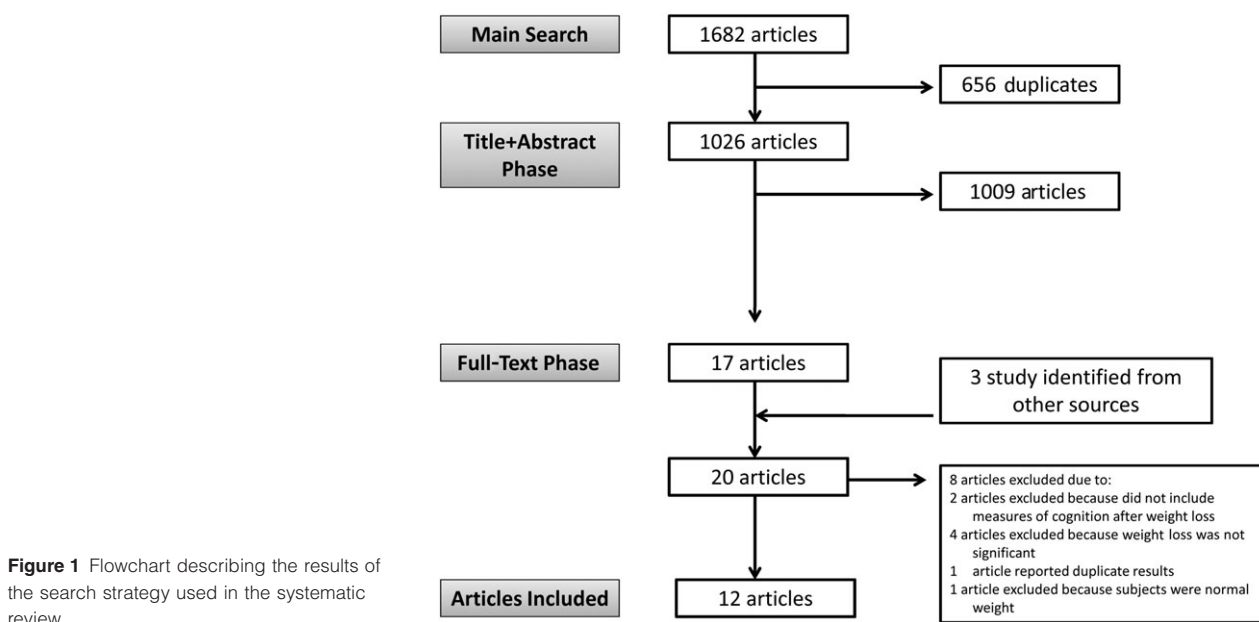
A meta-analysis was also conducted using data from the selected weight-loss studies (randomized and non-randomized) including a control group in their design (42,43,45–48). The analysis was performed to provide a more robust estimate of the effect size of weight loss on cognition compared to a weight maintenance group exposed to the same research environment and using the same methodology for the measurement of the research outcomes (body composition, metabolic, cognition) (results are shown in the *Supporting information*).

Results

In total, 1026 articles were identified after exclusion of 656 duplicates. Seventeen articles were considered eligible following title and abstract screening and three articles were identified from other sources. Following full-text review, 12 were selected for the final analysis as outlined in Fig. 1. Agreement between the two investigators was high for title–abstract phase ($n = 1026$, $\kappa = 0.89$, $P < 0.001$). One contentious paper (49) was selected in the final full-text stage ($n = 20$, $\kappa = 0.86$, $P < 0.001$) following resolution.

Description of studies

Seven studies (42,43,46,50–53) were randomized trials and three (42,43,46) of these included a weight maintenance control group. Five studies (44,45,47–49) had a non-randomized weight-loss study design and three (45,47,48) included a control group (Table 1). Subject age ranged from 20 to 80 years and the majority of studies ($n = 7$) (42,43,45,48,50,52,53) were conducted on middle-aged individuals (40–60 years), while five studies recruited women only (45–47,49,53). Only one study (48) recruited older subjects (average 60 ± 7 years, range 50–80 years). Average BMI ranged from overweight (26.1 kg m^{-2}) to morbid obesity (45.5 kg m^{-2}). Average study duration ranged from 28 days to 12.8 months. Four studies were excluded either because the effects of dieting rather than weight loss on cognitive function were investigated or because the amount of weight loss at the end of the intervention was statistically not significant and less than 2 kg (18,54–56).

Figure 1 Flowchart describing the results of the search strategy used in the systematic review.

Weight-loss interventions

Weight-loss interventions differed in their level of negative energy balance and dietary macronutrient composition. Four studies used a fixed energy intake for every participant ranging from very restrictive (600 kcal d^{-1}) (53) to moderate caloric restrictions ($\approx$1600 kcal d^{-1}) (48,50,52). Four studies individualized energy intake by applying a pre-defined level of caloric restriction (range 20% to 50%) to baseline energy requirement (42,45,47,51). Bariatric surgery was used in one study (44). A combined strategy using dietary patterns (dietary approach to stop hypertension diet) and behavioural and lifestyle modifications was used in one study (43).

Assessment of cognition

Primary outcome was assessed using a wide variety in number and type of cognitive tests used within and between studies as outlined in Table 1. In total, 29 different cognitive tests were administered covering a range of cognitive domains including memory, attention and executive performance. Of all tests, Digit Span (Forward/Backward) was the most commonly applied, being administered in five studies (43,45,48,50,52), followed by the Trail Making Test in four studies (43,45,48,53).

Effects of weight loss on cognitive function

Memory
Effects of weight loss on memory function were assessed in most studies (*n* = 7) (42,43,45–48,51). Results, however, were inconsistent as summarized in Table 2 and Fig. 2.

Average effects sizes were overall positive. However, confidence intervals were wide and results were generally not significant. Only two studies found a beneficial, significant effect of weight loss on memory performance (43,48). Smith *et al.* (43) measured memory function using the Verbal Paired Associates test and found an increase in SMD of 0.36 compared to baseline (95% CI = 0.06, 0.67, *P* = 0.01) in 43 overweight and obese hypertensive subjects. The effect size was larger (SMD = 0.66, 95% CI = 0.18, 1.15, *P* < 0.001) in Witte *et al.*'s study (48) using the Rey Auditory and Verbal Learning Test in 20 older-aged subjects (mean age: 60 years). Results from the meta-analysis random-effects model were significant, despite most studies finding non-significant results (SMD = 0.13, 95% CI = 0.00, 0.26, *P* = 0.04). This is possibly due to the large sample size of Smith *et al.*'s study (43) and the greater effect size observed in Witte *et al.*'s study (Table 2, Fig. 2). The exclusion of the two studies (42,43) having a weight loss plus exercise intervention in their protocol reduced the effect size and the model became marginally not significant (SMD = 0.12, 95% CI = −0.009, 0.26, *P* = 0.06). The effect size was heterogeneous between studies (*I*^{2} = 81.0%, *P* < 0.001) and this is not unexpected given the large differences in study design, duration of interventions, patient characteristics (age, BMI), weight-loss strategies, changes in body weight and inconsistent assessment of cognitive function. A subgroup analysis based on the stratification of the studies by baseline BMI status (overweight or obesity) revealed a potential interaction between weight loss and memory function by BMI group, with a tendency to observe positive effects of weight loss on memory with increasing baseline BMI (Table S2). The stratification, however, did not reduce heterogeneity (*I*^{2} > 80%). Lastly, when investigating the effect of weight loss on

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Table 1 Study design, methodology, weight-loss intervention, cognitive assessment, amount of weight loss and main results of the studies selected for the final phase of the systematic review and meta-analysis

Author, year and place	Sample specifics (study design, characteristics of the sample)	Weight-loss intervention	Cognitive tasks	Weight loss (kg)	Findings
Brinkworth *et al.*, 2009 (50), Australia	One-year, two-arm, randomized, non-controlled, parallel weight-loss intervention; 118 obese men and women (baseline BMI: 33.7 ± 0.4 kg m^{-2}; age: 50.0 ± 0.8 years) were randomized to two groups; 57 were assigned to the first group (G1) and 61 were assigned to the second group (G2); 58% and 65% of subjects in G1 and G2 groups completed the study respectively.	G1: LC diet (C = 4%, P = 33%, F = 61%). G2: LF diet (C = 46%, P = 24%, F = 30%). EI was approximately 1433 kcal d^{-1} for women and 1672 kcal d^{-1} for men.	Digit Span Backwards; Inspection Time Test.	G1: 13.7 (S*). G2: 13.7 (S*).	Significant improvement in DSB scores in both groups. Significant decline in speed of processing after 8 weeks but rebound after 1 year in both groups. Inverse correlation between change in DSB scores and change in fasting insulin levels after 52 weeks.
Cheatham *et al*, 2009 (51), USA	One-year, two-arm, non-controlled, randomized, parallel weight-loss intervention; 42 overweight men and women divided in two groups. First group (G1, *n* = 20) had baseline BMI of 27.7 ± 1.7 kg m^{-2} and age of 34.9 ± 4.3 years. Second group (G2, *n* = 22) had baseline BMI of 27.9 ± 1.4 kg m^{-2} and age of 34.6 ± 5.5 years.	G1: High GI (C = 60%; P = 20%; F = 20%). G2: Low GI (C = 40%; P = 30%; F = 30%). CD of both diets of about 20% relative to baseline.	Grammatical Reasoning; Four Choice Visual Reaction Time Task; Repeated Acquisition Test; Scanning Visual Vigilance Test.	G1: −8.5 ± 4.5% (S*). G2: −8.9 ± 5.4% (S*).	Weight loss was not associated with any change in cognitive function.
Green *et al.* 2005 (46), USA	Eight weeks, three-arm, controlled, randomized, parallel weight-loss intervention; 56 overweight and obese women with age range 20–45 years. Control group (Cn, *n* = 16) had baseline BMI of 26.8 ± 6.5 kg m^{-2}. Second group (G1, *n* = 25) had BMI of 28.1 ± 4.1 kg m^{-2}. Third group (G2, *n* = 14) has a BMI of 29.2 ± 6.5 kg m^{-2}.	Cn: Weight maintenance. G1: Unsupported diet (CR: −557 kcal d^{-1}). G2: Supported diet (CD: −553 kcal d^{-1}).	Two-Finger Tapping Task; Verbal Free Recall Task; Bakan Task; Mental Rotation Task; Simple Reaction Time; The Tower of London Task.	Cn: −0.04 ± 2.8 (NS). G1: −2.1 ± 7.2 (S*). G2: −2.6 ± 3.2 (S*).	The study matches the criteria for inclusion in the systematic review but missing data did not allow the inclusion of this study in the meta-analysis. Improvement in vigilance and immediate recall in Cn and G2 and decline in G1. Impaired performance on the Tower of London Task in G1. These impairments occurred only after 1 week of dieting and by the end of 8 weeks of dieting there were no differences in task performance between supported and unsupported dieting.

Table 1 *Continued*

Author, year and place	Sample specifics (study design, characteristics of the sample)	Weight-loss intervention	Cognitive tasks	Weight loss (kg)	Findings
Halyburton *et al.*, 2007 (52), Australia	Eight weeks, two-arm, non-controlled, randomized, parallel weight-loss intervention; 93 overweight and obese men and women divided in two groups. First group (G1, *n* = 48) had baseline BMI of 33.3 ± 0.6 kg m^{-2} and age of 50.6 ± 1.1 years. Second group (G2, *n* = 45) had baseline BMI of 33.8 ± 0.6 kg m^{-2} and age of 49.8 ± 1.3 years.	G1: LC diet (C = 4%, P = 33%, F = 61%). G2: LF diet (C = 46%, P = 24%, F = 30%). EI was approximately 1433 kcal d^{-1} for women and 1672 kcal d^{-1} for men.	Digit Span Backwards; Inspection Time Test.	G1: −8.0 ± 0.3% (S*). G2: −6.2 ± 0.4% (S*).	Significant decrease in IT in both groups but LF promoted greater improvements than LC. The difference was still significant after controlling for weight loss. The change in IT test scores was significantly positively correlated with energy from fat and negatively correlated with energy from carbohydrate. Significant improvement in DSB scores in both groups.
Martin *et al.*, 2007 (42), USA	Twenty-four weeks, randomized, controlled trial (CALERIE Study); 48 overweight men and women were divided in four groups (12 subjects per group). First group (Cn) had baseline BMI of 27.8 ± 0.6 kg m^{-2} and age of 37.0 ± 2.1 years. The second group (G1) had baseline BMI of 27.8 ± 0.4 kg m^{-2} and age of 39.0 ± 1.5 years. The third group (G2) had baseline BMI of 27.5 ± 0.5 kg m^{-2} and age of 36.0 ± 1.6 years. The fourth group (G3) had baseline BMI of 27.7 ± 0.5 kg m^{-2} and age of 38.0 ± 2.2 years.	Cn: Weight maintenance. G1: 25% CR. G2: 12.5% CR + EX + 12.5% PAL. G3: LCD (890 kcal d^{-1}) until 15% weight loss, followed by weight maintenance.	Rey Auditory and Verbal Learning Test; Auditory Consonant Trigram; Benton Visual Retention Test; Conners' Continuous Performance Test-II.	Cn: −1.0 ± 1.1% (NS). G1: −10.4 ± 0.9% (S*). G2: −10.0 ± 0.8% (S*). G3: −13.9 ± 0.7% (S*).	Weight loss was not associated with a consistent pattern of deficits in verbal memory, visual memory or attention/concentration performance.

Table 1 Continued

Author, year and place	Sample specifics (study design, characteristics of the sample)	Weight-loss intervention	Cognitive tasks	Weight loss (kg)	Findings
Smith et al., 2010 (66), USA	Four-month, three-arm, randomized, controlled trial (ENCORE Study): 124 overweight and obese moderately hypertensive men and women were divided in three groups. First group (DASH + WM, n = 43) had baseline BMI of 32.8 ± 4.1 kg m⁻² and age of 52.9 ± 10.4 years. The second group (DASH, n = 38) had baseline BMI of 32.8 ± 3.4 kg m⁻² and age of 52.3 ± 9.5 years. The third group (Cn) had baseline BMI of 32.7 ± 3.9 kg m⁻² and age of 51.7 ± 9.0 years.	DASH + WM: DASH diet and also participated in a behavioural weight management programme consisting of supervised aerobic exercise (three times per week) and weekly behaviour modification. DASH: DASH diet but did not exercise or lose weight. Cn: Weight maintenance.	Trail Making Test; Stroop Interference Test; Digit Span; Verbal Fluency Test; Verbal Pair Associates; Controlled Oral; Word Association Test; Ruff 2 and 7 Test; Digit Symbol Substitution Test.	DASH + WM: 8.9 (S*). DASH: 0.8 (NS). C: 0 (NS).	Information on the macronutrient composition and energy content of the diets was not available. DASH + WM group exhibited improvements in Trail Making Test B-A, Verbal Paired Associates, the Stroop Test and Ruff 2 and 7 tests compare to the control group but results were comparable to the DASH group. Subjects with greater atherosclerotic risk (higher intima-media thickness) exhibited greater improvements in cognitive function after weight loss. Association between weight loss and cognitive function may be confounded by exercise.
Wing et al., 1995 (53), USA	Twenty-eight days, two-arm, non-controlled, randomized parallel weight-loss intervention; 21 obese women divided in two groups. First group (G1, n = 11) had baseline BMI of 41.2 ± 1.9 kg m⁻² and age of 46.8 ± 2.2 years. Second group (G2, n = 20) had baseline BMI of 40.7 ± 2.2 kg m⁻² and age of 49.8 ± 2.5 years.	G1: LC-K (594 kcal d⁻¹; C = 7%, P = 35%, F = 58%). G2: HC-NK (590 kcal d⁻¹; C = 51%, P = 34%, F = 15%).	Stroop Interference Test; The Digit Vigilance Task; Trail Making Task.	G1: −8.4 ± 0.3 (S*). G2: −7.8 ± 0.4 (S*).	Improvement with weight loss on the Trail Making Task and the Stroop Color Word Test. There was a significant interaction between diet and weight loss on the Trail Making Task after 1 week (poorer performance of LC-K).
Bryan et al., 2001 (45), USA	Twelve weeks, non-randomized, controlled, parallel weight-loss intervention; 63 overweight and obese women subjects divided in two groups. First group (Cn, n = 21) had baseline BMI of 35.2 ± 4.8 kg m⁻² and age of 50.9 ± 7.3 years. Second group (G1, n = 42) had baseline BMI of 34.1 ± 4.3 kg m⁻² and age of 48.9 ± 8.2 years.	Cn: Weight maintenance. G1: 20% EI deficit; F = 15%.	Digit Symbol-Coding; Trail Making Test; Self-Ordered Pointing Task; Initial Letter Fluency and Excluded Letter Fluency; Stroop Interference Test; Digit Span Backwards Test; Rey Auditory and Verbal Learning Test.	G1: −7.9 ± 2.1 (S*). Cn: +0.10 (NS).	Reduction in number of intrusions made during recall measured by the RAVLT test in the G1 group. No other cognitive effects.

Table 1 Continued

Author, year and place	Sample specifics (study design, characteristics of the sample)	Weight-loss intervention	Cognitive tasks	Weight loss (kg)	Findings
Buffenstein et al., 2000 (49), South Africa	Nine overweight women participated in a 4-week, non-randomized weight-loss study. Baseline BMI of 26.1 ± 2.9 kg m⁻². Age range: 20–36 years.	EI: 800 kcal d⁻¹.	Assessment of hand–eye coordination performance using two computerized tests (Simple Reaction Test and Complex Reaction Task).	−5.8 ± 1.6 kg ($P < 0.05$).	Significant improvement in mean reaction time and number of correct hits with the Complex Reaction Task.
Guldstrand et al., 2003 (44), Sweden	Eight severely obese men and women (BMI: 45.5 ± 4.5 kg m⁻²) undergoing bariatric surgery. Age range: 26–55 years. Reassessment after an average follow-up of 12.8 ± 5.6 months.	Vertical banded gastroplasty.	Perceptual Maze Test (PMT) assessing inspection rate, processing rate, check time, left/right-hand preference, motor time and number of rubs out.	−39.8 ± 9.1 ($P < 0.001$).	Increase in processing and inspection speed and a decrease in motor times and number of rubs out.
Kretsch et al, 1997 (47), USA	Twenty-one weeks, two-arm, controlled, non-randomized, parallel weight-loss intervention; 25 obese women divided in two groups. First group (G1, n = 14) had baseline BMI of 31.5 ± 4.1 kg m⁻² and age of 35.0 ± 5.2 years. Second group (Cn, n = 11) had baseline BMI of 34.2 ± 1.5 kg m⁻² and age of 30.1 ± 7.5 years.	Cn: Weight maintenance. G1: 50% CR. Macronutrient composition was: C = 53%; F = 27%; P = 20%.	Bakan Vigilance Task; Word Recall Task; Simple Reaction Time; Two Finger Tapping Task; Ericksen effect.	Cn: Weight stable (NS). G1: −12.3 ± 5.5 (S*).	Significant increase in Simple Reaction Time at the end of caloric restriction. The two-second word-recall task was significantly improved. Word-recall scores were significantly correlated with body-weight changes at 5 weeks but not at 10 or 15 weeks of CR.
Witte et al., 2009 (48), Germany	Twelve weeks, controlled, non randomized, three-arm parallel weight-loss intervention; 50 normal-weight to obese men and women were divided in three groups. Mean age range of the population was 60.5 ± 7.6 years (range: 50–80 years). First group (Cn, n = 10) had baseline BMI of 27.4 ± 0.4 kg m⁻². The second group (G1, n = 20) had baseline BMI of 29.9 ± 3.8 kg m⁻². The third group (G2, n = 20) had baseline BMI of 26.9 ± 3.2 kg m⁻².	Cn: Weight maintenance (EI = 2100 kcal d⁻¹). G1: 30% CR (EI = 1630 kcal d⁻¹). G2: ↑20% PUFA (EI = 2209 kcal d⁻¹).	Rey Auditory and Verbal Learning Test; Trail Making Task; Digit Forward/Backward Span.	Cn: +0.8 ($P = 0.43$). G1:−2.4 ($P = 0.005$). G2:−1.0 ($P = 0.13$).	Significant improvement on RAVLT performance (more words and fewer errors) in the CR group. No significant changes in Trail Making Task or Digit Span were found. Changes in RAVLT scores were inversely correlated with changes in insulin and hs-CRP.

(S*): statistically significant but P-value not reported.
↑, 20% increase in dietary PUFA intake; BMI, body mass index; C, carbohydrate; CD, caloric deficit; CR, caloric restriction; CR + EX, caloric restriction plus exercise; DASH, dietary approach to stop hypertension; EI, energy intake; F, fat; GI, glycaemic index; HC-NK, high carbohydrate non-ketogenic; hs-CRP, high-sensitivity C-reactive protein; IT, inspection time; LC, low carbohydrate; LCD, low-calorie diet; LC-K, low-carbohydrate ketogenic; LF, low fat; P, protein; PAL, physical activity level; PUFA, polyunsaturated fatty acids; WM, weight management.
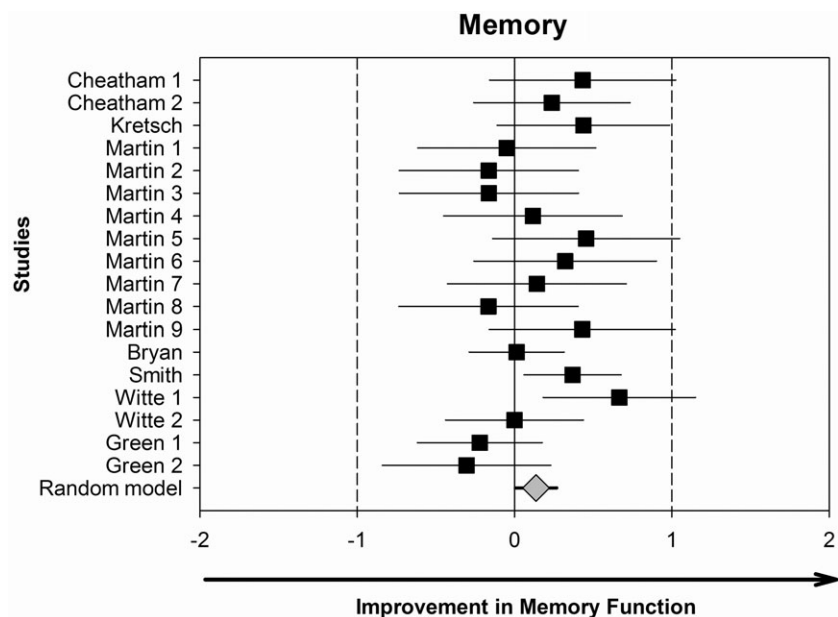
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Table 2 Meta-analysis of memory domains reporting the effects of weight loss in each study for each individual measure of cognition

Study name (indicated by first author)	Weight-loss group	Cognitive test	Standardized mean of the difference	Standard error	95% CI lower limit	95% CI upper limit	P-value
Cheatham 1	High GI	RA	0.43	0.30	−0.15	1.02	0.15
Cheatham 2	Low GI	RA	0.23	0.25	−0.25	0.73	0.34
Kretsch	CR	WR	0.43	0.28	−0.11	0.98	0.11
Martin 1	CR	RVALT	−0.05	0.28	−0.61	0.51	0.86
Martin 2	CR + EX	RVALT	−0.16	0.29	−0.73	0.40	0.57
Martin 3	LCD	RVALT	−0.16	0.29	−0.73	0.40	0.57
Martin 4	CR	ACT	0.11	0.29	−0.45	0.68	0.68
Martin 5	CR + EX	ACT	0.45	0.30	−0.13	1.05	0.13
Martin 6	LCD	ACT	0.32	0.29	−0.25	0.90	0.27
Martin 7	CR	BRVT	0.14	0.29	−0.42	0.71	0.62
Martin 8	CR + EX	BRVT	−0.16	0.29	−0.73	0.40	0.56
Martin 9	LCD	BRVT	0.43	0.30	−0.16	1.02	0.15
Bryan	CR	FRL	0.01	0.15	−0.28	0.31	0.92
Smith	DASH + BM	VPA	0.36	0.15	0.06	0.67	0.01
Witte 1	CR	RVALT	0.66	0.24	0.18	1.15	<0.001
Witte 2	CR	FDS	0.00	0.22	−0.43	0.43	1.00
Green 1	CR-supported	IVR	−0.22	0.20	−0.61	0.17	0.27
Green 2	CR-unsupported	IVR	−0.30	0.27	−0.84	0.23	0.26
Random model			0.13	0.06	0.00	0.26	0.04

The description of each test is reported in the *Supporting information* of this manuscript. However, for clarity, the unit and the direction of the effect associated with improvements of cognitive functions is reported.
ACT, Auditory Consonant Trigram; BRVT, Benton Visual Retention Test; CR, caloric restriction; CR + EX, caloric restriction plus exercise; DASH, dietary approach to stop hypertension; DASH + BM, dietary approach to stop hypertension plus behavioural modification; FDS, Forward Digit Span; FRL, free recall list; GI, glycaemic index; IVR, immediate verbal recall; LCD, low-calorie diet; RA, repeated acquisition; RVALT, Rey Auditory and Verbal Learning Test; VPA, Verbal Pair Associates; WR, word recall.

Figure 2 Forest plot of weight-loss studies reporting cognitive measures of memory function before and after weight loss. The details of each individual test are reported in Tables 1 and 2. Positive values of the effect size are associated with improvements in cognitive function.

memory function only in studies with a control group, the results were not significant (Table S4). The results did not change when the two studies including the weight loss plus exercise interventions (42,43) were excluded. The Funnel graph showed a symmetric distribution of the studies (Fig. S1).

Summary of findings. Effects of weight loss on memory function are heterogeneous. Weight loss had a modest but significant effect on memory performance in overweight and obese subjects. The magnitude of the effect appeared to be directly associated with baseline BMI. Furthermore, the effect disappeared when studies without a control group

were excluded suggesting that effects on cognition may not be entirely attributable to weight loss and changes in cognition may be occurring in response to the fact that individuals are enrolled in a research study (Hawthorne effect).

Attention/executive function

No single test to measure attention and executive function was applied consistently across studies. The Trail Making Test was the most applied (four studies) (43,45,48,53) followed by the Stroop Color Word (43,45,53) and the Simple/Complex Reaction Time (three studies) (46,47,49) (Table S1). The results derived from all attention–executive domain tests were pooled (Table 3, Fig. 3). Weight loss was found to be associated with a low order, significant improvement in attention and executive function (random model, SMD = 0.14, 95% CI = 0.01, 0.27, $P < 0.001$). The exclusion of the studies including an exercise intervention (42,43) and using bariatric surgery as weight-loss treatment (44) did not modify the results (SMD = 0.23, 95% CI = 0.08, 0.38, $P = 0.003$). Overall, five studies (45,46,50, 52,53) found a beneficial effect of weight loss on executive–attention domains and three studies (45,46,51) reported negative effects.

The strongest effect was found in the study by Wing *et al.* (53), which showed larger post-weight loss effect sizes using the Stroop (SMD = 4.35, 95% CI = 2.35, 6.36, $P < 0.001$) and Trail Making Test (SMD = 3.39, 95% CI = 1.78, 5.00, $P < 0.001$). The Funnel graph clearly identified these two data points as outliers which may have produced a biased estimate of the effect size (Fig. S2). The removal of these studies improved the symmetry of the distribution but reduced the pooled effect size (random model, SMD = 0.11, 95% CI = –0.007, 0.22, $P = 0.06$) (Table S8, Fig. S3). However, when stratifying the results by baseline BMI category, a significant effect of weight loss on attention/executive function was observed in obese subjects (*n* = 12 studies) (random model, SMD = 0.24, 95% CI = 0.09, 0.39, $P < 0.001$) and the effect size was not modified by the exclusion of the outliers (Tables S3 and S8). In contrast, the results were not significant in the overweight studies (*n* = 5 studies) (random model, SMD = –0.02, 95% CI = –0.26, 0.22, $P = 0.89$). The effect of weight loss on attention/executive cognitive function was still significant after exclusion of studies without a control group (44,49–53), and again when stratifying by BMI category the model was significant in studies with obese participants but not in those including overweight subjects (Table S5). The exclusion of the studies with an exercise intervention (42,43) and bariatric surgery as weight-loss treatment (44) did not modify the results.

Summary of findings. The results indicate a significant positive effect of weight loss on attention and executive function. Large variability in the results was observed which may reflect the diversity of tests used. The magnitude of the effect could be directly associated with baseline BMI.

Discussion

Studies were characterized by large heterogeneity in sample size, dietary intervention, follow-up interval, cognitive assessment protocol and sample characteristics. Despite these differences, more than 70% (9/12) of studies reported an improvement in some area of cognitive function (43–48,50,52,53). A low-order beneficial effect on memory and attention/executive function after weight loss was observed, generally in obese subjects. The effects of weight loss on attention/executive function were confirmed after exclusion of studies without a control group in their study design and after exclusion of the studies with an exercise intervention or bariatric surgery as weight-loss treatment.

An association between weight loss and better cognitive outcomes was related to baseline BMI (43–45,47, 50,52,53). A significant change in at least one cognitive function was identified when baseline BMI was in the obese range (BMI $\geq$ 30 kg m^{-2}) (43–45,47,50,52,53), with improvements less consistent in overweight subjects (BMI < 30 kg m^{-2}) (42,46,48,49,51). Overall, the results suggest that where the aim is to improve health and cognitive outcomes the primary target group should be obese individuals. This does not, however, detract from the health benefits of weight loss in overweight individuals.

Overall, the rate and magnitude of weight loss, the duration of the weight-loss interventions and dietary macronutrient composition did not appear to be associated with changes in cognitive function. However, the heterogeneity of the study design, dietary interventions and measurement protocols did not allow a formal analysis of the independent effects of these predictors on changes in cognitive function. Rather, the association between improvements in insulin sensitivity and improved cognition (48,50) suggests a possible mechanistic role of insulin resistance in cognitive decline. The role of insulin resistance was supported by the inverse association between insulin resistance and memory function (48,50) and by a trend in the association between improvements in cognitive function and weight loss in studies with greater baseline BMI. Greater insulin resistance was associated with an Alzheimer disease-like pattern of reduced cerebral glucose metabolic rate measured by positron emission tomography in adults with pre-diabetes and newly diagnosed type 2 diabetics (57). These results suggest that lifestyle modifications such as weight loss or physical exercise may be effective therapeutic strategies to prevent Alzheimer disease (58) due to the established effects on insulin sensitivity (59) and endothelial function (12,60). Furthermore, obesity has been associated with brain volume deficits in regions important for cognitive
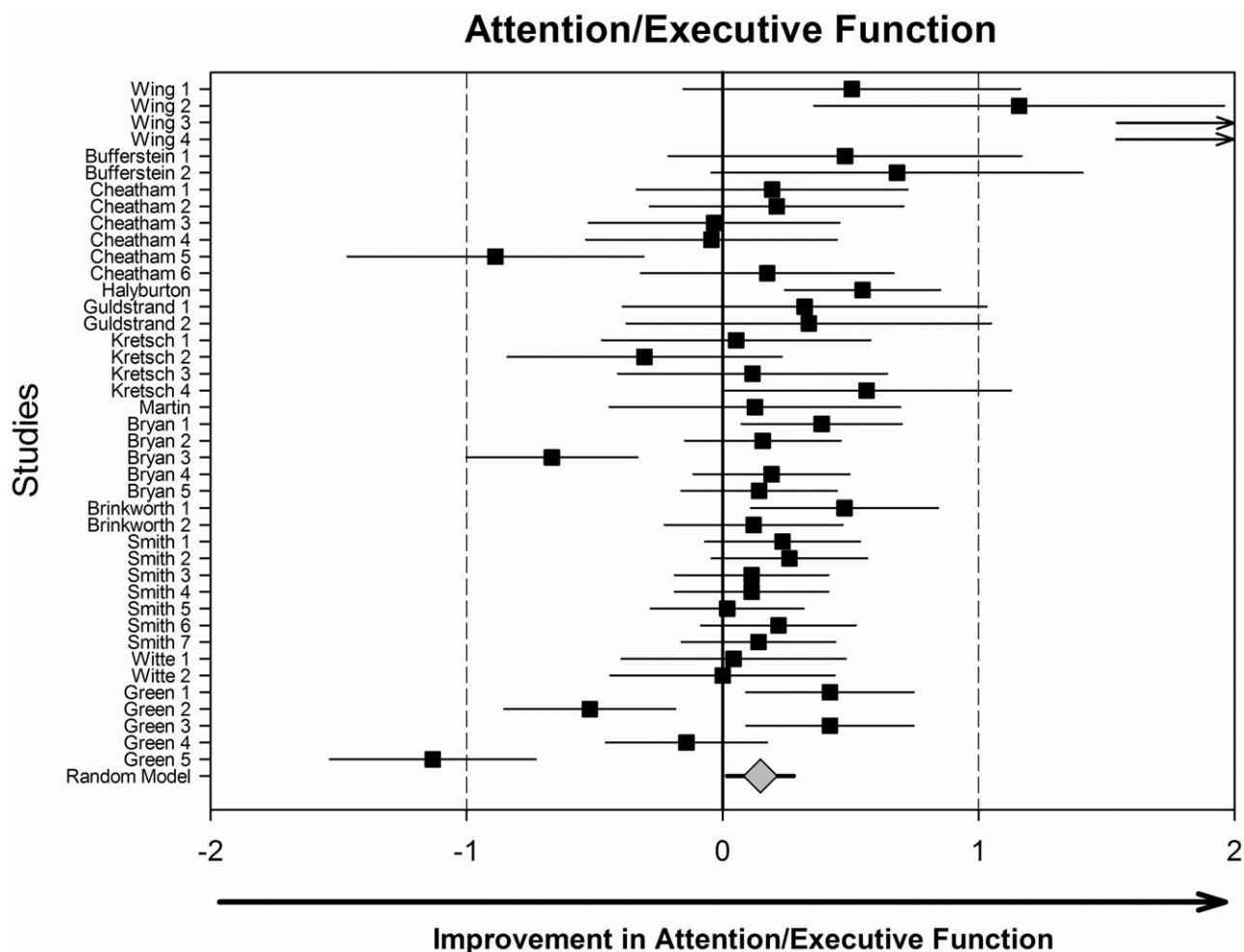
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Table 3 Meta-analysis of executive–attention domains reporting the effects of weight loss in each study for each individual measure of cognition

Study name (indicated by first author)	Weight-loss group	Cognitive test	Standardized mean difference	Standard error	95% CI lower limit	95% CI upper limit	*P*-value
Wing 1	Average (LC-K, HC-NK)	DVT (↑)	0.50	0.33	−0.15	1.16	0.13
Wing 2	Average (LC-K, HC-NK)	DVT (↓)	1.15	0.40	0.35	1.96	0.005
Wing 3	Average (LC-K, HC-NK)	ST	4.35	1.02	2.35	6.36	<0.001
Wing 4	Average (LC-K, HC-NK)	TMT	3.39	0.82	1.78	5.00	<0.001
Buffenstein 1	CR	S-C-MRT (↑)	0.47	0.35	−0.21	1.16	0.17
Buffenstein 2	CR	S-C-MRT (↓)	0.68	0.37	−0.04	1.40	0.06
Cheatham 1	Average (L-GI diet, H-GI diet)	GR (↑)	0.19	0.27	−0.33	0.72	0.47
Cheatham 2	Average (L-GI diet, H-GI diet)	GR (↓)	0.21	0.25	−0.28	0.70	0.40
Cheatham 3	Average (L-GI diet, H-GI diet)	FCRT (↑)	−0.03	0.25	−0.52	0.45	0.89
Cheatham 4	Average (L-GI diet, H-GI diet)	FCRT (↓)	−0.04	0.25	−0.53	0.44	0.86
Cheatham 5	Average (L-GI diet, H-GI diet)	VV (↑)	−0.88	0.29	−1.46	−0.30	0.003
Cheatham 6	Average (L-GI diet, H-GI diet)	VV (↓)	0.17	0.25	−0.32	0.66	0.48
Halyburton	Average (LC diet, LF diet)	IT	0.54	0.15	0.24	0.85	<0.001
Guldstrand 1	BS	PMT (↑)	0.32	0.36	−0.39	1.03	0.37
Guldstrand 2	BS	PMT (↓)	0.33	0.36	−0.37	1.04	0.35
Kretsch 1	CR	BT	0.05	0.26	−0.47	0.57	0.84
Kretsch 2	CR	SRT	−0.30	0.27	−0.84	0.23	0.26
Kretsch 3	CR	TT	0.11	0.26	−0.40	0.64	0.66
Kretsch 4	CR	EE	0.56	0.28	−0.001	1.12	0.05
Martin	Average (CR, CR + EX, LCD)	CPT	0.12	0.29	−0.44	0.69	0.66
Bryan 1	CR	DSC	0.38	0.16	0.07	0.70	0.01
Bryan 2	CR	TMT	0.15	0.15	−0.14	0.46	0.31
Bryan 3	CR	ST	−0.66	0.17	−1.00	−0.33	<0.001
Bryan 4	CR	Letter Fluency	0.19	0.15	−0.11	0.49	0.22
Bryan 5	CR	DSB	0.14	0.15	−0.16	0.44	0.35
Brinkworth 1	Average (LC diet, LF diet)	DSB	0.47	0.18	0.11	0.84	0.01
Brinkworth 2	Average (LC diet, LF diet)	IT	0.12	0.17	−0.22	0.46	0.49
Smith 1	DASH + BM	DSST	0.23	0.15	−0.06	0.53	0.13
Smith 2	DASH + BM	Ruff 2 and 7	0.26	0.15	−0.04	0.56	0.09
Smith 3	DASH + BM	TMT	0.11	0.15	−0.18	0.41	0.45
Smith 4	DASH + BM	WAT	0.11	0.15	−0.18	0.41	0.45
Smith 5	DASH + BM	ANT	0.01	0.15	−0.28	0.31	0.90
Smith 6	DASH + BM	ST	0.21	0.15	−0.08	0.52	0.15
Smith 7	DASH + BM	DSB	0.14	0.15	−0.16	0.44	0.359
Witte 1	CR	TMT	0.04	0.22	−0.39	0.48	0.84
Witte 2	CR	DSB	0.00	0.22	−0.43	0.43	1.00
Green 1	Average (CR-S, CR-Un)	BT	0.41	0.16	0.09	0.74	0.01
Green 2	Average (CR-S, CR-Un)	SRT	−0.51	0.17	−0.85	−0.18	0.002
Green 3	Average (CR-S, CR-Un)	MRT	0.41	0.16	0.09	0.74	0.01
Green 4	Average (CR-S, CR-Un)	FTT	−0.14	0.16	−0.45	0.17	0.38
Green 5	Average (CR-S, CR-Un)	TLT	−1.13	0.20	−1.53	−0.73	<0.001
Random model			0.14	0.06	0.01	0.27	<0.001

The description of each test is reported in the *Supporting information* of this manuscript. However, for clarity, the unit and the direction of the effect associated with improvements of cognitive functions is reported.

↑, increase in scores associated with improved cognitive performance; ↓, decrease in scores associated with improved cognitive performance. ANT, animal-naming test; BS, bariatric surgery; BT, Bakan test; CPT, Conners' Continuous Performance Test; CR, caloric restriction; CR + EX, caloric restriction plus exercise; CR-S, caloric restriction-supported; CR-Un, caloric restriction-unsupported; DASH, dietary approach to stop hypertension; DASH + BM, dietary approach to stop hypertension plus behavioural modification; DSB, Digit Span Backwards; DSC, digit symbol coding; DSST, digit symbol substitution test; DVT, digit vigilance test; EE, Ericksen effect; EI, energy intake; FCRT, four-choice reaction time; FTT, finger-tapping task; GR, grammatical reasoning; HC-NK, high carbohydrate non-ketogenic; H-GI, high-glycaemic index; IT, inspection time; LC, low carbohydrate; LCD, low-calorie diet; LC-K, low carbohydrate ketogenic; LF, low fat; L-GI, low glycaemic index; MRT, mean reaction time; PMT, Perceptual Maze Test; S-C-MRT, simple–complex mean reaction time; SRT, simple reaction time; ST, Stroop Test; TLT, Tower of London Test; TMT, trail making test; TT, tapping time; VV, visual vigilance; WAT, word association test; WM, weight management.

Figure 3 Forest plot of weight-loss studies reporting cognitive measures of attention–executive function before and after weight loss. The details of each individual test are reported in Tables 1 and 3. Positive values of the effect size are associated with improvements in cognitive function.

function (e.g. hippocampus – memory; anterior cingulate – executive function) in non-demented older-aged individuals (61). Similar but weaker effects have been found in overweight individuals (61). These results support neuroimaging findings from younger obese cohorts (62,63). The mechanisms by which obesity influences brain structure are unknown but may be linked to increased vascular and metabolic insult mediated by increased oxidative stress or inflammation (64). Weight loss may therefore mitigate these effects.

Stability of improved cognitive function following weight loss has not been investigated. An important research question is whether the effects are transient or, as previously suggested (48), represent a Hawthorne effect from increased social interaction in the enriched research environment typical of research investigations. Regular physical exercise has beneficial effects on cognitive function (65,66) and may be an important confounding factor mediating weight loss–cognition associations. This issue

was formally investigated in one study and the results were non-significant (42). Six studies accounted for the confounding effects of physical activity (42,45,47,50,52) in their study design whereas the remaining five (44,46,48,51,53) did not. However, the association between weight loss and cognition was overall equally distributed between the two groups of studies, which suggests a minimal impact of physical activity adjustment on the estimate of the effect size. Two studies included physical activity in the weight-loss strategy (42,43) and here it may have confounded the association between weight loss and cognition. However, the exclusion of the two studies from the analyses did not modify the effect of weight loss on the attention–executive domain whereas a marginal decrease in the effect size was observed for the memory domain.

Cognitive function was typically assessed immediately following weight loss, potentially confounding metabolic vs. body composition effects on changes in cognitive performance. Metabolism and hemodynamic fluxes, improving

brain functioning (19), are rapidly altered during negative energy balance. Reduced adiposity following longer periods of energy imbalance could also improve neuronal activities by favourably modifying the secretion and biological activity of hormones such as insulin, leptin and adiponectin, and reducing inflammatory and oxidative loads (67). However, information on the precise timing of the assessments and standardization of the measurement protocols after weight loss was incomplete. One study attempted to standardize the post-weight-loss assessment by performing cognitive measurements following an overnight stay at the research centre immediately after the weight-loss phase (51). The only study to test effects of short-term (energy flux perturbations) and long-term (body composition) weight loss on cognition-included psychological assessments both immediately after weight loss and after 3 weeks on a weight maintenance diet (47). The results were difficult to interpret as motor skills (simple reaction time) was significantly slower at the end of caloric restriction and continued to slow further during the weight stabilization period, whereas memory function (word recall) improved after weight loss, but returned to baseline levels during stabilization (47). This issue requires further research.

Heterogeneity was also observed in the effects of weight loss on cognition as contrasting results were reported within the same study (44,47). A more consistent negative effect on cognitive function following weight loss was found in one study (46). Relative to a control and supported dieting group who showed no changes in executive function or working memory (46), an unsupported dieting group had impaired executive function following weight loss. The authors concluded this group suffered more intrusive diet-related thinking, limiting the allocation of intellectual resources to the cognitive tasks. The results suggest that in order to minimize negative cognitive consequences of dieting, a weight-loss intervention should be implemented alongside dietetic and behavioural support. However, this was only tested in one study and future studies are warranted to determine the most effective weight-loss intervention to maximize compliance in addition to health and cognitive outcomes.

Obesity in middle age is associated with increased dementia risk (3) but this association is reversed in older subjects as an inverse relationship of BMI with dementia risk has been reported (68,69). The paradoxical interaction derives from an increased prospective dementia risk in both middle-aged underweight and obese subjects compared to normal weight (70,71). BMI is, however, an imperfect measure of excess adiposity as it does not provide information on fat and lean tissue masses or their regional distribution (72). Central adiposity has an important role in explaining the mechanistic and epidemiological associations between obesity and cardio-metabolic risk (73), and likewise shows more consistent, age-independent associations with dementia (74).

The study has several potential limitations. The meta-analyses are based on retrospective analytical inference which may be affected by the quality of the studies included, inclusiveness of the search strategy and publication bias. The clear delineation of a priori inclusion and exclusion criteria and a comprehensive search on electronic databases and reference lists would have minimized bias and increased the representativeness of the results. A robust selection procedure was particularly important in the identification of studies exploring relationships between eating behaviour (dieting, restraint), macronutrient modifications (glycaemic index) and cognitive function. In absence of a significant weight loss, these studies were excluded as they could not contribute to the investigation of the hypothesis underpinning this meta-analysis of an association between weight loss-induced improvements in metabolic health and modifications of cognitive performance. Large heterogeneity was observed in all aspects of the studies ranging from study design, type and duration of weight-loss interventions to choice of neuropsychological tests. In addition, the differences in study design and the lack of randomized, controlled clinical trials (only two studies) justified a broader selection of weight-loss studies to investigate the effects of weight loss on cognition. Therefore, the emphasis of the research question was on the evaluation of the changes in cognitive scores after significant weight loss in each study. The analysis was also based on the imputation of pre–post weight loss correlation of cognitive scores. A correlation value of 0.50 was chosen as a default value in order to avoid any differential bias. The sensitivity analysis confirmed that the random model became not significant only at correlation values below 0.50 for memory and 0.25 for attention/executive functions. Experimental data showed that pre–post weight loss correlations for memory tasks was 0.72 (verbal recall) and ranged between 0.31 (Tower of London Task) and 0.92 (Tapping Task) for tests assessing attention/executive function (average correlation value: 0.62) (M. Green, personal communication). Therefore, a correlation value of 0.50 was likely to provide a conservative estimate of the pooled effect size of weight loss on cognition.

The obesity paradox of dementia is not unique as a controversial role of increased adiposity in older populations has been described for other conditions (heart failure, osteoporosis) (75,76), generating more cautious nutritional and clinical approaches for obesity management in older age (77). Nevertheless, epidemiological evidence of secular increases in obesity prevalence in older subjects (78) and increased cardio-metabolic risk linked to excess adiposity (78) essentially reinforces the role of prevention and treatment of excess adiposity at younger ages, in order to reduce the tracking effects of fatness with ageing. A recent randomized clinical trial has demonstrated the positive effects of moderate weight loss and exercise on body composition, cardio-respiratory fitness and physical function, which

essentially supports the high benefit/risk ratio of lifestyle changes associated with moderate weight loss in obese older subjects (79). Whether the beneficial effects of weight loss can be extended to cognitive function remains to be determined.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Funnel plot of the effects of weight loss on memory domain.
Figure S2. Funnel plot of the effects of weight loss on attention/executive domain. The two outliers refer to the results by Wing *et al*. The Funnel plot after excluding the outliers is described in Fig. S3.
Figure S3. Funnel plot for the attention–executive domain after exclusion of the two outliers.
Table S1. Cognitive tests used in the studies included in this systematic review. Study reference numbers refer to the numerical order of the study presented in Table 1.
Table S2. Meta-analysis of memory domains reporting the effect sizes (ES) of weight loss in each study for each individual measure of cognition. The meta-analysis has been stratified by baseline body mass index (BMI) in obesity and overweight.
Table S3. Meta-analysis of attention/executive function domains reporting the effect sizes (ES) of weight loss in each study for each individual measure of cognition. The meta-analysis has been stratified by baseline body mass index (BMI) in obesity and overweight.
Table S4. Meta-analysis of weight-loss studies including a control group as part of the study design and reporting the effect sizes (ES) of weight loss on memory domains in each study for each individual measure of cognition.
Table S5. Meta-analysis of weight-loss studies including a control group as part of the study design and reporting the effect sizes (ES) of weight loss on attention/executive domains in each study for each individual measure of cognition.
Table S6. Memory domain. Sensitivity analysis using multiple imputations of pre–post weight loss coefficient of correlation (r) to evaluate changes in effect size (ES) of the meta-analysis random models.
Table S7. Attention/executive domain. Sensitivity analysis using multiple imputations of pre–post weight loss coefficient of correlation (r) to evaluate changes in effect size (ES) of the meta-analysis random models.
Table S8. Effect sizes (ES) of the fixed and random models for the effects of weight loss on attention/executive domain after exclusion of two outliers reported in Fig. S2.

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