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Author: Nicola Veronese Silvia Facchini Brendon Stubbs Claudio Luchini Marco Solmi Enzo Manzato Giuseppe Sergi Stefania Maggi Theodore Cosco Luigi Fontana

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WEIGHT LOSS IS ASSOCIATED WITH IMPROVEMENTS IN COGNITIVE FUNCTION AMONG OVERWEIGHT AND OBESE PEOPLE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Nicola Veronese[1,2*], Silvia Facchini[1*], Brendon Stubbs[3,4,5*], Claudio Luchini[6,7], Marco Solmi[2,8], Enzo Manzato[1,9], Giuseppe Sergi[1], Stefania Maggi[9], Theodore Cosco[10], Luigi Fontana,[11,12,13]

[1] Department of Medicine, DIMED, University of Padova, Padova, Italy.
[2] Institute of clinical Research and Education in Medicine (IREM), Padova, Italy
[3]Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom.
[4] Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, Box SE5 8AF, United Kingdom.
5 Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, UK
[6] Unit of Surgical Pathology, Santa Chiara Hospital, Trento, Italy.
[7]Department of Pathology and Diagnostics, Verona University and Hospital Trust, Verona, Italy.
[8] Department of Neurosciences, University of Padua, Via Giustiniani, 5, 35128 Padova, Italy.
[9] Aging Section, Institute of Neurosciences, Italian Research Council, Padova, Italy.
[10] MRC Unit for Lifelong Health and Ageing, London, UK.
[11] Division of Geriatrics and Nutritional Sciences and Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO, USA.
[12]Department of Clinical and Experimental Sciences, Brescia University, Brescia, Italy.
[13] CEINGE Biotecnologie Avanzate, Napoli, Italy.

Correspondence to: Nicola Veronese, Department of Medicine, Geriatrics Division, University of Padova, Via Giustiniani, 2 35128 Padova, Italy. Tel: +00390498218492; fax: +00390498211218; e-mail: ilmannato@gmail.com.

[*] Authors equally contributed to this research

Highlights:

- In our meta-analysis, weight loss was associated with an improvement in attention and memory.
- Executive function and language improved in longitudinal and RCT studies, respectively.
- Intentional weight loss should be promoted in obese/ overweight people

ABSTRACT (164/170)

Whilst obesity is associated with a higher risk of cognitive impairment, the influence of weight loss on cognitive function in obese/overweight people is equivocal. We conducted a meta-analysis of randomized controlled trials (RCTs) and longitudinal studies evaluating the influence of voluntary weight loss on cognitive function in obese/overweight individuals. Articles were acquired from a systematic search of major databases from inception till 01/2016. A random effect meta-analysis of weight loss interventions (diet, physical activity, bariatric surgery) on different cognitive domains (memory, attention, executive functions, language and motor speed) was conducted. Twenty studies (13 longitudinal studies=551 participants; 7 RCTs= 328 treated vs. 140 controls) were included. Weight loss was associated with a significant improvement in attention and memory in both longitudinal studies and RCTs, whereas executive function and language improved in longitudinal and RCT studies, respectively. In conclusion, intentional weight loss in obese/ overweight people is associated with improvements in performance across various cognitive domains. Future adequately powered RCTs are required to confirm/ refute these findings.

Keywords: cognition; memory, attention, weight loss; obesity; meta-analysis, physical activity, nutrition

1. INTRODUCTION

The prevalence of overweight and obesity is high and increasing in all age groups, including the elderly (Nguyen and El-Serag, 2010; WHO consultation, 2000). Several medical complications are associated with excessive adiposity, including type 2 diabetes (Chan et al., 1994), cardiovascular diseases (Eckel, 1997), cancer (Renehan, Nature Review Cancer 2015), cognitive impairment (Xu et al., 2011), and premature mortality (Fontana and Hu, 2014; Ng et al., 2014).

Weight loss remains the cornerstone for the treatment of obesity, and can be achieved through several interventions, such as calorie restriction and/or physical exercise, and in extreme cases bariatric surgery. Weight loss is associated with improvements in multiple metabolic factors (i.e. glucose tolerance, insulin sensitivity, blood pressure, oxidative stress, and inflammation), which have been implicated in the pathogenesis of cognitive impairment and dementia (Ceriello et al., 2014; Bennett et al., 2009; Schmidt et al., 2002).

However, the potential cognitive benefits of weight loss are still unclear and largely limited to those associated with weight loss from physical activity alone. Higher physical activity level seems to be able to increase gray and white matter volume in the prefrontal cortex (Colcombe et al., 2006) and is associated with greater sparing of prefrontal and temporal brain regions (Erickson et al., 2010). Moreover, exercise training increases cerebral blood volume (Burdette et al., 2010) and perfusion of the hippocampus (Pereira et al., 2007), one of the most important organ in the control of food intake. If these anatomical changes correspond to better cognitive function is, however, not fully understood.

A previous systematic review and meta-analysis with a search date of over 5 years ago (Siervo et al., 2011) found that weight loss had a beneficial effect on some cognitive domains, particularly among obese individuals. Whilst this previous study advanced the field, the authors relied on conclusions based on observational studies and did not include data from randomized control trials (RCTs). Whilst inferences from observational data are helpful, the certitude of any relationship between weight loss and cognition from such data is limited. RCTs enable causal inferences to be asserted and therefore, a meta-analysis of interventional data may offer additional information beyond that of observational data. Moreover, these authors did not investigate the influence of different weight loss strategies on cognitive performance outcomes. Understanding the potential impact of different weight loss strategies would offer new and important information.

We therefore aimed to investigate the effect of intentional weight loss on cognitive status assessed through validated scales in overweight and obese people across observational and interventional studies. We hypothesized that weight loss would be beneficial for cognition in obese/overweight individuals.

2.MATERIALS AND METHODS

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria (von Elm et al., 2008) and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement (Liberati et al., 2009).

2.1 Search strategy

Two investigators (NV, SF) independently conducted an electronic literature search using EMBASE, PubMed and Scopus with no language restrictions, from their inception until 02/01/2016, searching studies providing data on intentional weight loss on cognitive parameters in obese and overweight people. Any inconsistency was resolved by consensus.

In PubMed, the following controlled vocabulary terms and keywords were considered: (obese or overweight) and (weight loss) and (cognit*).

A similar search strategy was performed in the other databases. Reference lists of the articles included in the analysis and of others papers relevant to the topic were hand-searched to identify additional, potentially relevant publications. Conference abstracts were also considered.

2.2 Study selection

We only considered studies that: (1) included overweight and obese people before any weight loss intervention, defined through a body mass index (BMI) between 25 and 29.9 and a BMI>30 kg/m^2 (WHO consultation,2000), respectively; (2) reported data on any cognitive domain (e.g. attention, executive function, memory, motor speed, language and global cognition) assessed through validated scales before and after a weight loss intervention program, (3) longitudinal or interventional studies using diet, calorie restriction, increased physical activity or bariatric surgery as interventions; (4) reported at least 2 Kg of weight loss (i.e. clinically significant weight loss) (Siervo et al., 2011) in the treated group between follow-up and baseline.

We excluded studies for the following reasons: (1) non validated scales for assessing cognition; (2) unintentional weight loss (i.e. not voluntary weight loss, for example due to an illness); (3) use of pharmacological interventions for losing weight; (4) no human subjects included.

Where data about baseline or follow-up tests were not available, the first and corresponding authors of each paper were contacted at least 4 times in a month period. All of the five authors we contacted gave us the additional information on the meta-analysis (see the Acknowledgments section).

2.3 Data extraction

Two authors (MS, CL) independently extracted data from the selected studies in a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (BS). The following information was extracted: i) characteristics of the study population (e.g. sample size, demographics, country in which the study was performed); ii) type of intervention (diet, calorie restriction, physical activity, bariatric surgery or mixed interventions); iii) mean duration of follow-up; iv) mean BMI at baseline and at follow-up; v) tests used for the assessment of cognitive status.

2.4 Outcomes

The primary outcomes were the results at follow-up evaluation of any cognitive tests assessed through validated scales. Cognitive tests were categorized according to their nature in global, attention, executive function, memory, motor speed, and language domains. For longitudinal studies, a comparison of the values between follow-up and baseline evaluations (with-in groups), while in randomized controlled trials a comparison between the final values of cognitive tests (among-groups analyses) were analyzed in line with the Cochrane reviewer handbook recommendations (Higgins and Green, 2008).

2.5 Assessment of study quality

Study quality was assessed by two investigators (SF, CL), while another one was available for mediation (NV).

For longitudinal studies, the Newcastle-Ottawa Scale (NOS) (Wells et al., 2012) was used to assess study quality. The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome.

The quality of RCTs was assessed through the Jadad’s scale (Jadad et al., 1996), although we did not consider blinding among the parameters of quality, having 3 points (2 for randomization and one for dropouts) consequently available.

2.6 Statistical analysis

The meta-analysis was performed using the Comprehensive Meta-Analysis 3.0 (CMA 3.0) [http://www.meta-analysis.com/index.php]. When combining studies, the random effect model was used to account for anticipated heterogeneity (DerSimonian and Laird, 1986). For cognitive data at follow-up, means and standard deviations (SD) at follow-up (compared to baseline in longitudinal and with the control group in RCTs) were analyzed to calculate standardized mean differences [SMD].

These estimates were calculated also for each type of intervention (diet, calorie restriction, physical activity, bariatric surgery or mixed interventions). All estimates were calculated together with 95% confidence intervals [CI].

Study heterogeneity was measured using the chi-squared and I-squared statistics, assuming that a $p \leq 0.05$ for the former and a value ≥50% for the latter indicated a significant heterogeneity (Higgins and Thompson, 2002). Since the previous meta-analysis by Siervo and colleagues (Siervo et al., 2011) suggested that the effect of weight loss on cognition was significant only in obese people, we tested if baseline BMI in longitudinal studies (or differences of BMI between treated and control groups in RCTs) could moderate our results.

Publication bias was assessed by visually inspecting funnel plots and by using the Begg-Mazumdar Kendall tau (Begg and Mazumdar, 1994) and the Egger bias tests (Egger et al., 1997). Additionally, to account for publication bias, we used the trim-and-fill method, based on the assumption that the effect sizes of all the studies were normally distributed around the center of a funnel plot; in the event of asymmetry, this method adjusts for the potential effect of unpublished (trimmed) studies (Egger et al., 1997). Finally, we calculated the fail safe number of negative studies that would be required to nullify each of our comparative analyses (i.e., result in $p>0.05$) (Rosenthal, 1979).

3. RESULTS

The search identified 1,674 potentially eligible studies, including 424 duplicate studies which were rejected. After excluding 1,209 papers on the grounds of a review of their titles and abstracts, 41 full-text articles were examined, and 20 studies were ultimately included in our meta-analysis (**Figure 1**) (Alosco et al., 2014; Boraxbekk et al., 2015; Brinkworth et al., 2009; Bryan and Tiggemann, 2001; Buffenstein et al., 2000; Cheatham et al., 2009; Green and Elliman, 2012; Guldstrand et al., 2003; Halyburton et al., 2007; Kretsch et al., 1997; Marques et al., 2014; Martin et al., 2009; Miller et al., 2013; Napoli et al., 2014; Prehn et al., 2016; Siervo et al., 2012; Smith et al., 2010; Spitznagel et al., 2014; Wing et al., 1995; Witte et al., 2009).

3.1 Study and patient characteristics

Study and patient characteristics are summarized in **Supplementary Table 1** (longitudinal studies) and **2** (RCTs).

The 13 longitudinal studies (Alosco et al., 2014; Boraxbekk et al., 2015; Brinkworth et al., 2009; Buffenstein et al., 2000; Cheatham et al., 2009; Guldstrand et al., 2003; Halyburton et al., 2007; Kretsch et al., 1997; Marques et al., 2014; Miller et al., 2013; Siervo et al., 2012; Spitznagel et al., 2014; Wing et al., 1995) included 551 participants, while the 7 RCTs (Bryan and Tiggemann, 2001; Green and Elliman, 2012; Martin et al., 2009; Napoli et al., 2014; Prehn et al., 2016; Smith et al., 2010; Witte et al., 2009) encompassed 468 individuals (328 in the treated groups and 140 controls), representing a total of 1,019 participants with obesity or being overweight at baseline. The mean age was 50.0 (standard deviation, SD=10.7) years, and the included participants were predominantly women (=78.3%).

The majority of these studies were conducted in North America (8 studies: 6 longitudinal and 2 RCTs), followed by 7 studies (3 longitudinal and 4 RCTs) performed in Europe, 3 in Oceania (2 longitudinal and one RCT), one longitudinal study in South Africa and another one in Brazil (**Supplementary Tables 1-2**). In only one study (Napoli et al., 2014), people older than 65 years of age were included.

The interventions used across the studies were diet (n=13 studies; 538 participants [326 in 8 longitudinal and 212 in 5 RCTs]), bariatric surgery (n=5 longitudinal studies with 225 participants) and multi-interventions in the remaining 2 RCTs with 116 participants (i.e. one group treated with diet, one with physical activity regimen or mixed intervention). A total of 140 participants were allocated to a control group (**Supplementary Tables 1-2**).

3.2 Longitudinal studies reporting on the effect of weight loss on cognition

The 13 longitudinal studies (Alosco et al., 2014; Boraxbekk et al., 2015; Brinkworth et al., 2009; Buffenstein et al., 2000; Cheatham et al., 2009; Guldstrand et al., 2003; Halyburton et al., 2007; Kretsch et al., 1997; Marques et al., 2014; Miller et al., 2013; Siervo et al., 2012; Spitznagel et al., 2014; Wing et al., 1995) followed-up 551 participants with a mean age of 46.3 (SD=12.8) years, predominantly women, for a median of 24 (range: 4-144) weeks. The BMI significantly decreased across the studies by 7 Kg/m^2 (from 37.2 at baseline to 30.9 at follow-up). The quality, assessed with the NOS, was moderate, with a median score of 6 (**Supplementary Table 1**).

Table 1 shows the results of weight loss interventions on cognition in prospective studies. Weight loss interventions improved attention domains in nine studies (Alosco et al., 2014; Buffenstein et al., 2000; Cheatham et al., 2009; Kretsch et al., 1997; Marques et al., 2014; Miller et al., 2013; Siervo et al., 2012; Spitznagel et al., 2014; Wing et al., 1995) involving 337 participants (SMD=0.30; 95%CI: 0.15-0.44, p<0.0001; I^2=64%), with the five studies using a dietary intervention (Buffenstein et al., 2000; Cheatham et al., 2009; Kretsch et al., 1997; Siervo et al., 2012; Wing et al., 1995). The dietary intervention impact on attention was more pronounced than the four (Alosco et al., 2014; Marques et al., 2014; Miller et al., 2013; Spitznagel et al., 2014) using bariatric surgery (diet: SMD=0.42; 95%CI: 0.13-0.71, p=0.005;

$I^2=58\%$; bariatric surgery: SMD=0.26; 95%CI: 0.08-0.44, p=0.004; $I^2=68\%$). Similar findings were evident for executive function. Seven studies exploring the effects of dietary calorie restriction (Alosco et al., 2014; Brinkworth et al., 2009; Cheatham et al., 2009; Guldstrand et al., 2003; Miller et al., 2013; Spitznagel et al., 2014; Wing et al., 1995) with 546 participants (SMD=0.49; 95%CI: 0.29-0.68, p<0.0001; $I^2=72\%$) showed a larger effect compared to bariatric surgery (diet: 388 participants; SMD=0.64; 95%CI: 0.32-0.96, p<0.0001; $I^2=79\%$; bariatric surgery: 158 participants; SMD=0.40; 95%CI: 0.16-0.64, p=0.001; $I^2=38\%$). Finally, weight loss induced primarily by dietary interventions seems to be associated with improved memory domains in five studies (Alosco et al., 2014; Boraxbekk et al., 2015; Kretsch et al., 1997; Miller et al., 2013; Spitznagel et al., 2014) (234 individuals; SMD=0.66; 95%CI: 0.48-0.83, p<0.0001; $I^2=63\%$) (**Table 2**).

Conversely, weight loss interventions did not significantly improve motor speed (7 studies only with dietary interventions; (Alosco et al., 2014; Buffenstein et al., 2000; Cheatham et al., 2009; Kretsch et al., 1997; Marques et al., 2014; Miller et al., 2013; Siervo et al., 2012; Spitznagel et al., 2014; Wing et al., 1995); SMD=0.13; 95%CI: -0.37-0.10, p=0.10; $I^2=69\%$) and language (3 studies only with bariatric surgery; (Alosco et al., 2014; Miller et al., 2013; Spitznagel et al., 2014); SMD=0.08; 95%CI: -0.06 to 0.22, p=0.27; $I^2=0\%$) parameters.

Publication bias seems to be unlikely for all the outcomes investigated and the trim and fill analysis did not significantly change our findings (**Table 2**). The failsafe number was over 200 for all significant outcomes.

3.3 Randomized controlled trials on the effect of weight loss on cognition

As shown in **Supplementary Table 2,** the seven RCTs (Bryan and Tiggemann, 2001; Green and Elliman, 2012; Martin et al., 2009; Napoli et al., 2014; Prehn et al., 2016; Smith et al., 2010; Witte et al., 2009) included 328 participants randomized to treated groups (262 in a dietary intervention group, 26 treated with physical activity, and 40 with both interventions).

The treated groups were on average 53.8 (SD=11.5) years old with two thirds being women (67.6%), which was similar to those randomized as controls (mean age, 53.9 (SD=12.7) years; women: 78.1%). After a median of 20 weeks of follow-up (range:8-48), the treated participants had a decrease of about 2.5 Kg/m^2 of BMI, while the controls only experienced a 1.0 Kg/m^2 reduction ($p<0.0001$ between groups). Regarding quality, using the Jadad's scale for this evaluation, one study reported 3 points over 3 available, one only one point and the others 2 points. Taking the controls as reference, four studies (Bryan and Tiggemann, 2001; Green and Elliman, 2012; Prehn et al., 2016; Napoli et al., 2014) reported a significant improvement in attention parameters in the treated group (222 treated vs. 104 controls; SMD=0.44; 95%CI: 0.26-0.62, $p<0.0001$; I^2=60%) (**Table 2**). However, only physical activity alone, and diet and physical activity together, were able to improve these outcomes in one study (Napoli et al., 2014).

Treated participants showed significant improvements in memory tests (Bryan and Tiggemann, 2001; Green and Elliman, 2012; Martin et al., 2009; Smith et al., 2010; Witte et al., 2009) (236 treated vs. 113 controls; SMD=0.35; 95%CI: 0.12-0.57, p=0.002; I^2=64%), particularly when diet and calorie restriction were used (204 treated vs. 113 controls; SMD=0.37; 95%CI: 0.09-0.35, p=0.01; I^2=71%). This outcome, however, seemed to be affected by publication bias (Egger's test=3.72±0.68; p=0.004), likely due to the inclusion of studies reporting negative findings. The trim and fill procedure, in fact, increased the SMD to 0.61 (95%CI: 0.37-0.86) with 3 studies trimmed (**Table 2**).

Finally, treated participants experienced a significant improvement in language parameters (4 studies (Bryan and Tiggemann, 2001; Prehn et al., 2016; Napoli et al., 2014; Smith et al., 2010) (222 treated individuals vs. 104 controls; SMD=0.21; 95%CI: 0.05-0.37, p=0.009; I^2=73%), particularly in one study using physical activity and a mixed intervention (Napoli et al., 2014). Language domains analysis suffered of publication bias as well, but the trim and fill procedure did not change our results (SMD=0.32; 95%CI: 0.03-0.61).

3.4 Descriptive findings

Few studies investigated the effect of weight loss on global scales of cognition. One RCT reported data on global aspects of cognition showing that the 3MS improved more in the diet, exercise, and diet-exercise groups than in the control group (Napoli et al., 2014). Similarly, the findings of a longitudinal study (Siervo et al., 2012) showed that weight loss was associated with significant improvements in Mini-Mental State Examination.

3.5 Meta-regression

Almost all the outcomes included in our meta-analysis revealed a moderate-high heterogeneity as indicated by I^2>50%. As shown in **Supplementary Table 4**, however, baseline BMI in longitudinal studies and differences in BMI between treated and control groups in RCTs did not moderate any of these outcomes.

4. DISCUSSION

In this meta-analysis involving 20 studies and more than 1,000 obese and overweight subjects, weight loss appears to confer a beneficial influence on cognitive function. Although our findings were heterogeneous, in longitudinal studies weight loss improved attention, executive function and memory, while in RCTs, weight loss also result in improved language items. The high failsafe number indicates that many negative studies would be required to nullify our main results (i.e. take p>0.05), indicating our results are robust. Altogether, our findings suggest that weight loss is associated with improvement in cognition. However, in the absence of large-scale clinical trials, our findings should be interpreted cautiously and it remains a challenge to decipher if the improvements in cognition are due to the respective interventions or weight loss itself.

Accumulating data suggest that overweight and obesity are associated with cognitive decline, and with a higher incidence of vascular dementia and Alzheimer's disease, particularly among middle aged subjects (Pedditizi et al., 2016). In a large systematic-review and meta-analysis of 21 studies and 62,425 individuals, being obese was associated with a ~40% increased risk of incident dementia in people below the age of 65 years, but the opposite was seen in those aged 65 and over, in which obesity reduced the risk of dementia of about 17% (Pedditizi et al., 2016). This finding agrees with our results, since the mean age of the subjects included in our analyses was about 50 years, and did not include any study made only in those over 65 years. Thus, the effect of weight loss may be particularly beneficial among middle-aged subjects at higher risk of poor cognitive status. Moreover, our data suggest that weight loss over a relatively shorter period of time can result in improvements in cognitive outcomes. However, whether or not weight loss interventions with diet and exercise in the long term can reduce the incidence of dementia specifically among obese people warrants further exploration. Within our analyses, it appears there might be some variation in the benefits induced by different weight loss interventions on cognitive performance. It appears, for example, that nutritional interventions have a particularly powerful influence in improving cognition outcomes across the longitudinal studies. Unfortunately, there was limited data on physical activity and cognitive outcomes in our data set, thus precluding any definitive conclusions regarding these outcomes in obese adults. Given this, there is a need for future studies to investigate the comparative effectiveness of different weight loss strategies on cognition, both in isolation and in combination. Such research should also seek to clarify the potential neurobiological mechanisms that underlie the observed improvements in cognition, since to date the exact mechanisms remain unclear.

Our data builds upon a previous systematic review in several ways (Siervo et al., 2011). First, our meta-analysis included 20 studies and over 1000 participant's, while Siervo et al. only included 12 studies and 343 participants. Moreover, our study investigated the influence of weight loss on several cognitive domains not previously considered (e.g. attention and executive functions as separated domains, and motor speed and language as new facets of cognition). Moreover, we accounted for publication bias, and investigated sources of heterogeneity with meta regression analyses. In addition, we considered data from RCTs, which enables stronger inferences to be made than relying purely on observational data. Finally, five author groups provided additional data for our meta-analysis, thus the current meta-analysis has advanced the field beyond the knowledge, which is publically available.

Intentional weight loss could be beneficial for overweight and obese subjects through several mechanisms. First, weight loss reduces insulin resistance which has been associated with poorer cognitive status (Biessels and Reagan, 2015). Insulin resistance, , is associated with lower cerebral glucose metabolism rate in pre-diabetic and diabetic subjects (Baker et al., 2011). Moreover, insulin regulates the activity of a number of brain areas relevant for memory, reward, eating behavior and the regulation of whole-body metabolism (Heni et al., 2015). Second, weight loss reduces inflammatory and oxidative stress, and increases serum adiponectin concentration. Inflammation and oxidative stress seem to play a pivotal role in the pathogenesis of cognitive decline (Bennett et al., 2009; Schmidt et al., 2002). Moreover, in Alzheimer's disease-transgenic mice adiponectin has been shown to be neuroprotective for hippocampal cells (Letra et al., 2014). Therefore, the modulation of these cytokines and adipokines through weight loss could contribute, at least in part, to the improvement in the cognitive tests observed in the treated subjects, and influence brain function and structure in obese and overweight subjects (Bischof and Park, 2015). Future research is required to disentangle the potential neurobiological mechanisms through which weight loss influences cognition.

The findings of our meta-analysis should be interpreted within its limitations. First, we were unable to assess the impact of weight loss on preventing dementia and Alzheimer’s disease due to the lack of data. Second, the mean duration of the studies was usually short, the sample was often limited in size, and a gender bias was present. Third, the great majority of the observational studies investigated the effect of dietary restriction or bariatric surgery, with few studies addressing the effect of physical activity programs on cognition. . Finally, many of the outcomes studied demonstrated to be moderate/highly heterogeneous, and our meta regression analyses could not completely explain. . Interestingly, the effect of weight loss on cognition seems not to be moderated by the baseline BMI, suggesting that weight loss is beneficial in both overweight and obese subjects.

In conclusion, our data suggest that intentional weight loss among obese and overweight individuals is associated with improvements in cognitive performance across different cognitive domains across observational studies and randomized clinical trials. More studies with a longer follow-up duration are required, with a particular emphasis on RCTs which seek to understand the neurobiological underpinnings of any improvements in cognition from weight loss. Such research should attempt to disentangle the extent to which improvements from weight loss are attributable to weight loss and individual intervention mechanisms. An area of interest might be whether weight loss in midlife can improve cognition sufficiently to prevent the onset of Alzheimer’s disease.

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Figure 1. PRISMA flow-chart

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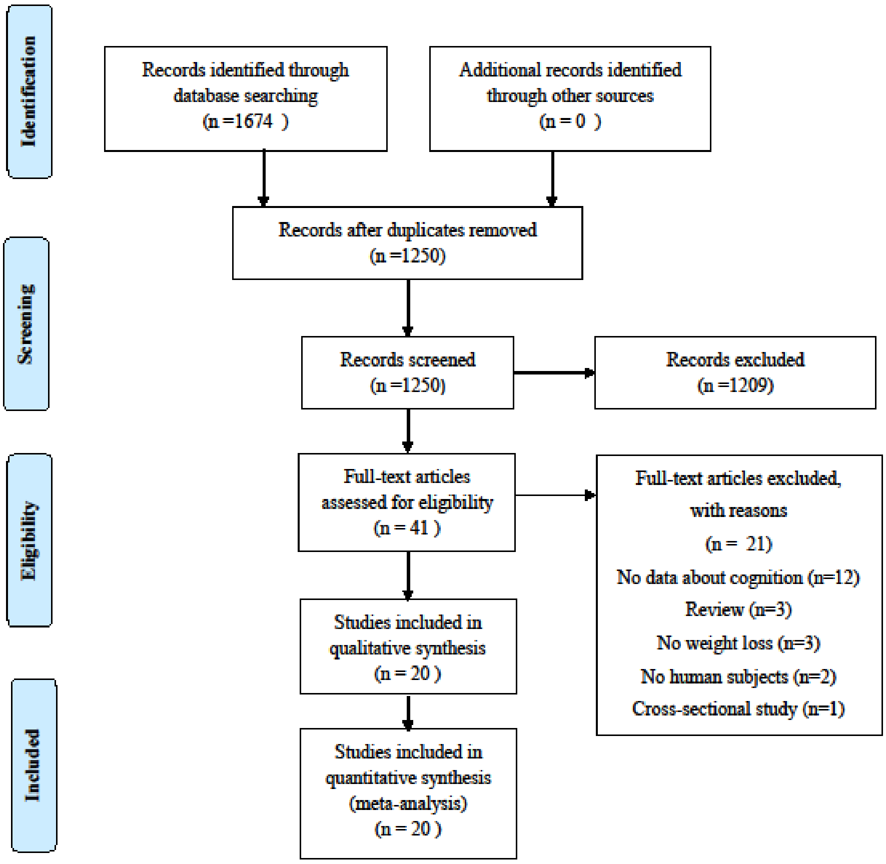

Table 1. Meta-analysis of longitudinal studies with publication bias assessment

Analysis	**Number of studies**	**Meta-analysis**					**Heterogeneity**	**Publication bias**		**Classic fail safe N**
		Participants	**SMD**	**95% CI**		**P value**	**I^2**	**Egger bias & p value**	**Trim and fill (95% CI)**	
Attention										
Total	9	337	**0.30**	**0.15**	**0.44**	**<0.0001**	64	-1.16; 0.27	0.19 (0.02 to 0.33)	270
Diet	*5*	*170*	***0.42***	***0.13***	***0.71***	***0.005***	*58*			
Bariatric surgery	*4*	*167*	***0.26***	***0.08***	***0.44***	***0.004***	*68*			
Executive function										
Total	7	546	**0.49**	**0.29**	**0.68**	**<0.0001**	72	-1.67; 0.34	0.57 (0.35 to 0.80)	230
Diet	*4*	*388*	***0.64***	***0.32***	***0.96***	***<0.0001***	79			
Bariatric surgery	*3*	*158*	***0.40***	***0.16***	***0.64***	***0.001***	38			
Memory										
Total	5	234	**0.66**	**0.48**	**0.83**	**<0.0001**	63	-0.11; 0.95	0.80 (0.61 to 0.95)	546
Diet	*1*	*20*	***0.67***	***0.22***	***1.12***	***0.003***	-			
Bariatric surgery	*4*	*214*	***0.68***	***0.49***	***0.88***	***<0.0001***	*71*			
Motor speed										
Total	7	496	0.13	-0.37	0.10	0.10	69	1.53; 0.41	0.18 (-0.03 to 0.41)	1
Diet	*7*	*496*	*0.13*	*-0.37*	*0.10*	*0.10*	*69*			
Bariatric surgery	No study available									
Language										
Total	3	200	0.08	-0.06	0.22	0.27	0	-2.57; 0.24	Unchanged	0
Diet	No study available									
Bariatric surgery	3	*200*	*0.08*	*-0.06*	*0.22*	*0.27*	*0*			

Abbreviations: SMD: standardized mean difference; CI: confidence interval.

Table 2. Meta-analysis of randomized controlled trials with publication bias assessment

Analysis	**Number of studies**	**Number participants**		**Meta-analysis**				**Heterogeneity**	**Publication bias**		**Classic fail safe N**
		Intervention	**Controls**	**SMD**	**95% CI**		**P value**	**I^2**	**Egger bias & p value**	**Trim and fill (95% CI)**	
Attention											
Total	4	222	104	**0.44**	**0.26**	**0.62**	**<0.0001**	60	-1.48; 0.73	Unchanged	52
Diet	*4*	*168*	*104*	*0.17*	*-0.07*	*0.42*	*0.16*	*40*			
Physical activity	*1*	*26*	*27*	***0.64***	***0.25***	***1.03***	***0.001***	*0*			
Diet + physical activity	*1*	*28*	*27*	***0.93***	***0.53***	***1.32***	***<0.0001***	*0*			
Executive function											
Total	2	99	56	-0.00	-0.38	0.37	0.97	41	Not possible		
Diet	*2*	*99*	*56*	*-0.00*	*-0.38*	*0.37*	*0.97*				
Memory											
Total	6	236	113	**0.35**	**0.12**	**0.57**	**0.002**	64	**3.72; 0.004**	**0.61 (0.37 to 0.86)**	116
Diet + CR	*6*	*204*	*113*	***0.37***	***0.09***	***0.65***	***0.01***	*71*			
CR + physical activity	*1*	*12*	*12*	*0.24*	*-0.16*	*0.64*	*0.24*	*0*			
UFA enhancement	*1*	*20*	*10*	*0.56*	*-0.21*	*1.34*	*0.15*	*0*			
Motor speed											
Total	2	117	50	0.17	-0.14	0.48	0.28	12	Not possible		
Diet	*2*	*105*	*50*	*0.12*	*-0.21*	*0.45*	*0.47*	*25*			
Diet + physical activity	*1*	*12*	*12*	*0.46*	*-0.35*	*1.27*	*0.27*	*0*			
Language											
Total	4	222	104	**0.21**	**0.05**	**0.37**	**0.009**	73	**8.92; 0.04**	**0.32 (0.03 to 0.61)**	15

Diet	*4*	*168*	*104*	*0.03*	*-0.14*	*0.21*	*0.71*	0
Physical activity	*1*	*26*	*27*	***1.20***	***0.62***	***1.79***	***<0.0001***	0
Diet + physical activity	*1*	*28*	*27*	***1.27***	***0.69***	***1.85***	***<0.0001***	0

Abbreviations: SMD: standardized mean difference; CI: confidence interval; CR: calorie restriction; UFA: unsaturated fatty acids.