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Changes in cognitive function following bariatric surgery: A Systematic Review

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(Review Article)

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Abstract

Background: Increased body mass is directly associated with reduced cognitive function. *Objectives:* The aim of this study was to systematically review the effect of bariatric weight loss surgery on cognitive function. *Methods:* A comprehensive and unrestricted literature search was conducted using the following databases: MEDLINE, EMBASE, PubMed, Scopus, Web of Sciences and the Cochrane Library. *Results:* A total of 414 publications were identified, of which 18 were included in the final review. Cognitive function as measured by a number of different assessment tools was shown to improve following surgically induced weight loss in most studies. *Conclusions:* Significant and rapid weight loss resulting from bariatric surgery is associated with prompt and sustained improvements in cognitive function including memory, executive function and cognitive control.

Introduction

There exists a direct relationship between increased body mass and widespread cognitive impairment.[1-6] Given that previously published meta-analyses have found a positive association between weight loss and cognitive function, it would be reasonable to hypothesize that weight loss surgery may reverse cognitive impairment in obese individuals.[7,8] The negative cognitive effects of obesity may relate to a number of factors associated with increase adiposity, including proinflammatory mediators and gut peptide hormone signaling.[9-12] This paper will review the current literature to examine the effects of bariatric surgery on neurocognitive function. The importance of obesity influencing neurocognitive decline is further magnified by the ever increasing incidence of cognitive impairment and neurodegenerative diseases such as Alzheimer's, for which obesity is also a significant risk factor.[13]

Objectives.

This systematic review aims to determine the effect of weight loss from bariatric surgery on different measures of cognition. This question will be addressed by a detailed analysis of the available literature to identify research participants who have undergone cognitive analysis both before and after weight loss surgery. The key strengths and limitations of different studies will be acknowledged along with any additional outcomes that are relevant to neurocognitive function. It is hoped that these findings will clarify if weight loss surgery reverses obesity-associated cognitive impairment.

Methods

Protocol and registration

This review was conducted in accordance with the PRISMA 2009 protocol, which is openly available from a number of sources. This review was registered through the PROSPERO Systematic Review Data Repository (SRDR) initiative (available at http://www.crd.york.ac.uk/PROSPERO accessed 2nd September 2015); the registration number is CRD42015025888.

Eligibility criteria

Studies in all languages were considered, with no restrictions placed on the date of publication, population demographics or duration of follow-up.

Search criteria

Searches were conducted using the following specialist search engines and databases: MEDLINE, PubMed, Scopus, Web of Science and The Cochrane Library. The date of the last search was 8th September 2015. During the searches, the following terms were used to describe surgery for weight loss: bariatric surgery, gastric surgery, gastric bypass, Roux-en-Y, gastric band, sleeve gastrectomy and weight loss surgery. The following terms were used to describe cognition: memory, cognition, cognitive function, dementia, Alzheimer's disease and Alzheimer's.

Study selection

All studies that measured at least one aspect of cognitive function both before and after surgery were included in the final review. This was regardless of their overall design or publication status. Titles and abstracts were first screened by 2 independent reviewers to be classified as relevant, possibly relevant or not relevant. Full text articles were then obtained for all relevant and possibly relevant titles. These were screened for eligibility and then analyzed thoroughly before being included in the final review (Figure 1). The reference lists of all these publications were further reviewed as an additional source of potentially relevant literature.

Data collection process and analysis

Data was extracted from each study based on a list of predetermined variables that included participants' age, gender, weight, type of surgery and performance on cognitive testing. Study characteristics such as the design and length of follow-up were also sought. Additional analysis was undertaken to determine the key strengths and limitations of each study along with its specific contribution to the current literature. The principal outcome measure was the change in performance on cognitive testing following weight loss surgery. While this may be perceived as quite a broadly defined measure to use, this approach was adopted due to the wide variation in methodologies with no two studies using the same type of cognitive assessment. Change in body mass index (BMI) was also recorded as a measure of weight loss and its potential to improve cognition. Numerical data collected from each study was then presented in a single table (Table 1) to give a clear overview of all the significant changes that occurred in cognitive assessment scores following bariatric surgery. A further table (Table 2) was required to clarify exactly what each of these changes represented and to also include any additional secondary findings that were relevant to neurocognitive function. Publications relating to the Longitudinal Assessment of Bariatric Surgery (LABS) study were grouped within their own subsection so as to clearly highlight that this data came from the same population sample followed up over a number of years.

Assessment of risk of bias

Risk of bias was assessed through analysis of the methodology and the results of each study. This included determining the original primary endpoints, identifying any missing data and reviewing the selection process for participants. This assessment was carried out by 2 independent reviewers and with reference to the risk of bias tools provided by the Cochrane Institution.[14]

Results

Study selection and characteristics

A total of 414 titles and abstracts were screened, from which 18 papers were included in the final review. Numerical data from 6 studies involving a total of 134 patients were included in Table 1. All of these studies had a prospective design, 3 of which included a control group. The mean postoperative weight change for all patients in Table 1 was a reduction in BMI of 8.87 Kgm^{-2} over an average follow-up period of 3.97 months. Twelve studies did not contain any numerical data relating to cognitive assessment and were therefore summarized and included in Table 2 only. Four additional review articles were also acknowledged and analyzed in order to contribute to the final discussion.[15-18]

Results of the effect of bariatric surgery on cognitive function

Methods of cognitive assessment varied considerably throughout studies which made it difficult to compare different cognitive performances. Guldstrand et al,[19] used the

Perceptual Maze Test, a marker of cognitive and perceptual functioning, to demonstrate a more impulsive and speed preferring strategy in postoperative patients. Marques et al,[20] was similarly able to show improved executive function following weight loss surgery as an improved score on the Trail Marking Test, an assessment of visual attention and task switching. The LABS dataset series of publications also showed significant improvements in predominantly memory domains and some aspects of executive function. These changes were most dramatic following a period of substantial weight loss shortly after surgery.

One well designed comparative cross-sectional study by Georgiadou et al,[21] of 50 post RYGB patients was unable to find any significant differences for a range of cognitive assessments and non-food related impulsivity scores when compared to well matched pre RYGB controls. This suggests that weight loss surgery causes subtle changes to longitudinal intra-individual variability on test performance in specific cognitive sub-scales that cannot be replicated by inter-group variability within well-matched cross-sectional samples. These small and specific changes in cognition would suggest a definite need for prospective and longitudinal study designs. This viewpoint has been further reinforced by Sousa et al,[22] who were similarly unable to observe any inter-group differences for five separate tests of executive function carried out in 30 obese subjects seeking bariatric surgery and 30 post bariatric surgery patients.

Risk of bias across studies

The LABS study is a multi-site, prospective, longitudinal study observing the effects of bariatric surgery on a single cohort over a substantial follow-up period of up to 48 months. Many publications have resulted from this dataset, which have advanced our current understanding of the long-term effects of bariatric surgery on cognition. However it is important to recognize the potential for these studies to introduce a certain level of bias to the current literature by over-representing a single patient population from which a large amount of data and publications have been produced.

Discussion

The studies included in this review demonstrate a consistent change in brain activation following surgically induced weight loss that is associated with improved cognitive control. We will now briefly explore some of the commonly suggested confounding factors that may also influence these changes. While there exists a much wider literature base for some of these topics, we have contained our current discussion to papers acknowledged by the studies included in this review.

Depression and Psychiatric Disorders

Many of the studies included in this review did screen for and exclude participants with major depressive disorders. This does not however exclude the possibility of other psychiatric symptoms influencing cognitive outcomes, as it is widely accepted that mood plays a major role in both executive function and cognitive performance in general.[23,24] A review of all studies that used a structured interview to diagnose psychopathology in patients undergoing bariatric surgery found that the point prevalence of any psychiatric disorder was 31.9% (range 24.1% to 37.8%) and 12.7% (range 10.9% to 15.6%) for mood disorder alone; these were considerably higher than rates of 26.2% for psychiatric disorder and 9.5% for mood disorder in a sample from the general United States population.[25] It is highly likely that this association between weight gain and low mood is reversible as positive changes in mood are often observed following active participation in weight loss programs.[26] One randomized trial of 194 obese participants showed a significant decrease in the mean Beck Depression Inventory (BDI-II) depression scores from 8.1 to 6.2 following weight loss by a number of methods.[27] With respect to specifically surgically induced weight loss, the point prevalence of depressive disorders has been shown to decrease significantly and there have also been reports of maintained improvements in psychological outcomes including self-esteem and depression for up to 4 years after bariatric surgery.[28,29] While it is possible that this high pre-surgery psychiatric comorbidity is therefore reduced slightly following surgical weight loss, the small size of this effect as demonstrated by BDI depression scores would be unable to account for the dramatic improvements in cognition demonstrated post weight loss surgery.

Physical Activity

Increased physical activity is another lifestyle factor that has been shown to have consistent and measurable positive influences upon cognition and brain function.[30,31] Multicenter patient data taken directly from the LABS project has shown that the majority of individuals increase their level of physical activity after bariatric surgery.[32] However, despite the possible confounding effect of physical activity on cognitive function, this could not be demonstrated in one particular study of 85 bariatric surgery participants which found that postoperative improvement in cognitive function was not associated with greater recorded physical activity.[33] This may be explained by the same data from the LABS project also observing that despite some slight improvements in physical activity, most patients still remained inactive after bariatric surgery and some even become less active.[32] To further determine the effect of exercise on postoperative cognitive changes it would therefore seem reasonable for any further research to include the monitoring of physical activity as part of the routine postoperative follow-up.

Medical Comorbidity

A number of obesity associated medical conditions such as type 2 diabetes, hypertension and sleep apnea have all been shown to cause measurable cognitive impairment.[34-39] Comprehensive meta-analyses have reported the resolution rates for these medical conditions post bariatric surgery as 78.1% for type 2 diabetes, 63.7% for hypertension and 85.7% for obstructive sleep apnea.[40-42] While there remains an accepted independent relationship between obesity and reduced cognitive function it is still possible that the resolution of these cognitively limiting medical conditions does influence postoperative cognitive improvements on a wider scale. However, in clinical practice, longitudinal data from the LABS project has been unable to observe any relationship between improvement in cognition and resolution of medical comorbidities including hypertension, diabetes, and sleep apnea.[43-45] This may have been due to lower than usual rates of comorbidity resolution or perhaps because the negative cognitive effects of these conditions are permanent and irreversible.

Thiamine Deficiency

A retrospective case series, found during this review, identified 570 bariatric surgery patients who had been evaluated by a neurologist postoperatively.[46] Twenty two of these patients were found to have new cognitive complaints and 10 had subsequent volumetric MRI scans which demonstrated focal thalamic atrophy predominantly in the posterior medial regions when compared with age and gender matched controls. These results were not typical of thiamine deficiency and further screening for nutritional deficiencies proved unremarkable. Three case reports also identified postoperative problems with cognition however these were due to confirmed Wernicke encephalopathy secondary to thiamine deficiency.[47-50] From the references of these publications a comprehensive systematic review was identified.[51] This review identified 84 cases of Wernicke encephalopathy post bariatric surgery. The vast majority occurred less than 6 months postoperatively (94%) and were associated with recurrent vomiting (90%). All of these cases involved either gastric bypass (51%), diverse restrictive procedures (44%) or biliopancreatic diversion (5%) and only half achieved complete recovery following treatment. Estimates of an incidence of Wernicke encephalopathy based on 2 studies of over 3,000 patients from Southern Europe gave a rate of around 1 in every 500 malabsorptive bariatric operations.[52,53]

Findings in Rodent Models

One particular study of obese rodent models compared weight loss through either RYGB, vertical sleeve gastrectomy (VSG) or caloric restriction and showed overall improvements in hippocampal-dependent learning as assessed for by the radial arm maze and spontaneous alternation tests.[54] Rodents subjected to VSG also exhibited small but significant deficits in relation to spatial learning tasks and elevated hippocampal inflammation which was unchanged by ghrelin replacement. Although these findings are limited to animal models, a difference in the effect of weight loss on cognition attributable to the specific type of surgical procedure itself does suggest an involvement of physiological, hormonal or nutritional pathways. In order for these mechanisms to be explored further it is therefore essential for future research to make direct comparisons between restrictive and malabsorptive procedures and the subsequent cognitive changes that result.

Summary of Evidence

Despite all these potentially confounding psychological and lifestyle factors, this review supports the view that there is a direct physiological role of weight loss surgery in influencing cognitive function. The authors of this review suggest that perioperative routine screening for bariatric surgery should include a cognitive assessment sensitive to executive function and memory. This would be justified clinically as it would identify both any improvement and, perhaps more importantly, any decline in cognition over time. One of the key strengths of this review is that it observes a number of substantial and rapid instances of weight loss. The considerable speed and size of these weight changes means that any direct effect on cognition should therefore be magnified and have a greater chance of being detected through generalized cognitive assessments.

Limitations

Due to the relatively short length of follow-up in most of the studies reviewed it is not possible to suggest any long-term effects of bariatric surgery on reducing the risk of developing neurodegenerative diseases such as Alzheimer dementia. Further larger prospective studies that involve the long term follow up of large numbers of bariatric surgery recipients with well matched controls will be required to answer this question

Conclusion

To our knowledge, this is the first published systematic review that examines the changes in cognitive function that occur following bariatric surgery. Overall this paper concludes that there is enough evidence to suggest a measurable improvement in cognitive function following bariatric surgery. This improvement would appear to be most prominent in the domains of memory and executive function, particularly cognitive control. These changes should not be viewed as simply due to a reduction in adipose tissue alone but more as the indirect result of complex homeostatic mechanisms possibly with some influence from lifestyle changes. While it may still be inappropriate to reference cognitive improvement as a reason to offer bariatric surgery, as a result of these findings it may now be more acceptable to list improved cognitive function as one of the auxiliary benefits of the procedure.

Conflict of Interests

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All applicable institutional and/or national guidelines for the care and use of animals were followed.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Key Words

Systematic review, bariatric surgery, gastric surgery, gastric bypass, Roux-en-Y, gastric band, sleeve gastrectomy and weight loss surgery, memory, cognition, cognitive function, dementia, Alzheimer's disease, Alzheimer's.

Table 1. Changes to scores of cognitive function following bariatric surgery

First author & year of publication	Study design	Sample size	Mean Age	Female:Male	Type of Surgery	BMI Pre-Surgery	BMI Post-Surgery	Δ BMI	Tool	Tool Subsection	Pre
Guldstrand 2003[19]	PCS	8	40 (26-55)	7:1	VBG	45.0 ±4.5	30.7 ±2.7	-14.3	PMT	Processing Rate	5.2 ±1.
										Inspection Rate	21. ±6.
										Motor time (ms)	46 ±3
										Max rows	13. ±1.
										Correct mazes (%)	80 ±1
										Rub outs	1.5 ±0.
Marques 2014[20]	PCS	17	40.5± 10.1	17:0	RYGB	50.1 ±4.7	37.2 ±4.1	-12.9	TMT	A-Time	48. ±1
										B-Time	14 ±1
										B-Error	1.9 ±2.
Longitudinal Assessment of Bariatric Surgery (LABS) Project Publications											
Gunstad 2011[55]	C-PCS	109	44.66±11.03	91:18	104 RYGB 5 LAGB	46.45 ±6.65	38.61 ±6.32	-7.84	Mem-ory	Learning (T-Score)	42. ±1
										Short Delay Free Recall (T-Score)	45. ±1
										Long Delay Recall (T-Score)	45. ±1
										Recognition (T-Score)	40. ±1
									Atten-tion	Switching of Attention (T-Score)	53. ±1

Miller 2013[56]	C-PCS	95	43.23±10.84	85:10	93 RYGB 2 LAGB	46.19 ±5.90	30.23 ±5.23	-15.96	Mem- ory	Leaning (T-Score)	42. ±12
										Long Delay Recall (T-Score)	45. ±10
										Recognition (T-Score)	41. ±10
Alosco 2014[43]	C-PCS	63	42.29±11.42	57:6	62 RYGB 1 LAGB	46.52 ±5.26	31.34 ±6.42	-15.18	Mem- ory	Total recall (T-Score)	46. ±14
										Long Delay recall (T-Score)	46. ±11
										Recognition (T-Score)	41. ±11
Alosco 2014[57]	PCS	50	44.08±10.76	46:4	49 RYGB 1 LAGB	46.61 ±5.27	32.35 ±6.57	-14.26		Attention (T-Score)	52. ±7.
										Executive Function (T-Score)	51. ±10
										Memory (T-Score)	44. ±10

BMI (Body Mass Index)
PCS: Prospective Cohort Study. C-PCS: Controlled Prospective Cohort Study.
VBG: Vertical banded gastroplasty. LAGB: Laparoscopic adjustable gastric banding. RYGB: Roux-en-Y gastric bypass.
PMT: Perceptual Maze Test. TMT: Trail Marking Test.
[1] n=16

Table 2. A summary of cognitive changes following bariatric surgery

First author & year of publication	Summary of postoperative cognitive changes and additional secondary findings
Guldstrand 2003[19]	Cognitive function appears to be clearly modified following weight loss from a more cautious accuracy pre preferring maze-solving strategy on the Perceptual Maze Test.
	Insulin sensitivity improved postoperatively along with a decrease in plasma C-Peptide, insulin and glucag counter regulatory responses during prolonged hypoglycaemia as shown by a decrease in epinephrine, no and cortisol.
Morton 2009[58]	Significant improvements in attention and memory (p<0.002), processing speed (p<0.03) and verbal learn months after laparoscopic gastric bypass.
Sousa 2012[22]	There were no significant differences in performance on five neuropsychological tests of executive functic participants seeking bariatric surgery and 30 post-bariatric surgery patients. Both groups performed belov
Marques 2014[20]	Improved postoperative scores on the Trail Marking Test, a measure of executive function and cognitive fl
Georgiadou 2014[21]	This comparative cross-sectional study of 50 post RYGB patients was unable to find any significant group c assessments and non-food related impulsivity scores when compared with a pre RYGB control group matc
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Gunstad 2011[55]	Before bariatric surgery there was an overall low to average performance in multiple cognitive domains in memory. 12 weeks post-surgery this improved to within the average or above average ranges.
	Patients without hypertension exhibited better postoperative cognitive performance than those with hyp
Miller 2013[56]	Bariatric surgery patients performed significantly better than obese controls at 12 months on the learning indices.
	Performance of obese controls on all indices at 12 months did not differ from baseline.
Spitznagel 2013[59]	Better cognitive function at 12 weeks post-surgery predicted a lower body mass index (BMI) in 57 bariatri months. This was possibly due to greater adherence.
Lavender 2014[60]	Lifetime history of binge eating disorder did not influence changes in BMI or cognitive function in 68 baria months.
Spitznagel 2014[61]	Better cognitive function at 12 weeks post-surgery predicted a lower BMI in 55 bariatric surgery patients f
Alosco 2014[43]	Significant improvements in various measures of memory were seen in 63 bariatric surgery patients follow
Alosco 2014[57]	Post bariatric surgery executive function and memory continued to improve over time up to 36 months w generally began to decline after 24 months.
	A smaller sample of 21 patients followed up to 48 months showed significant improvements from baselin
Alosco 2014[62]	Postoperative decreases in alkaline phosphatase (ALP) and a lower baseline cystatin C were associated wi bariatric surgery patients followed up at 12 months.
Alosco 2014[63]	Age did not influence changes to cognitive performance in 95 bariatric surgery patients followed up at 12
Alosco 2014[64]	Family history of Alzheimer's disease was associated with postoperative cognitive impairment and a failur in 94 bariatric surgery patients followed up at 12 weeks.

Alosco 2015[65]	Pre-operative history of major depressive disorder did not influence baseline or postoperative changes to in 67 bariatric surgery patients followed up at 12 months.
Alosco 2015[66]	Decreases in leptin and increases in ghrelin were associated with improvements in attention and executiv patients followed up at 12 months. These improvements were not influenced by BMI which may imply tha ghrelin may instead be responsible for obesity related declines in cognitive function.
Hawkins 2015[67]	Changes to CRP levels were not associated with changes to cognitive function in 77 bariatric surgery patie

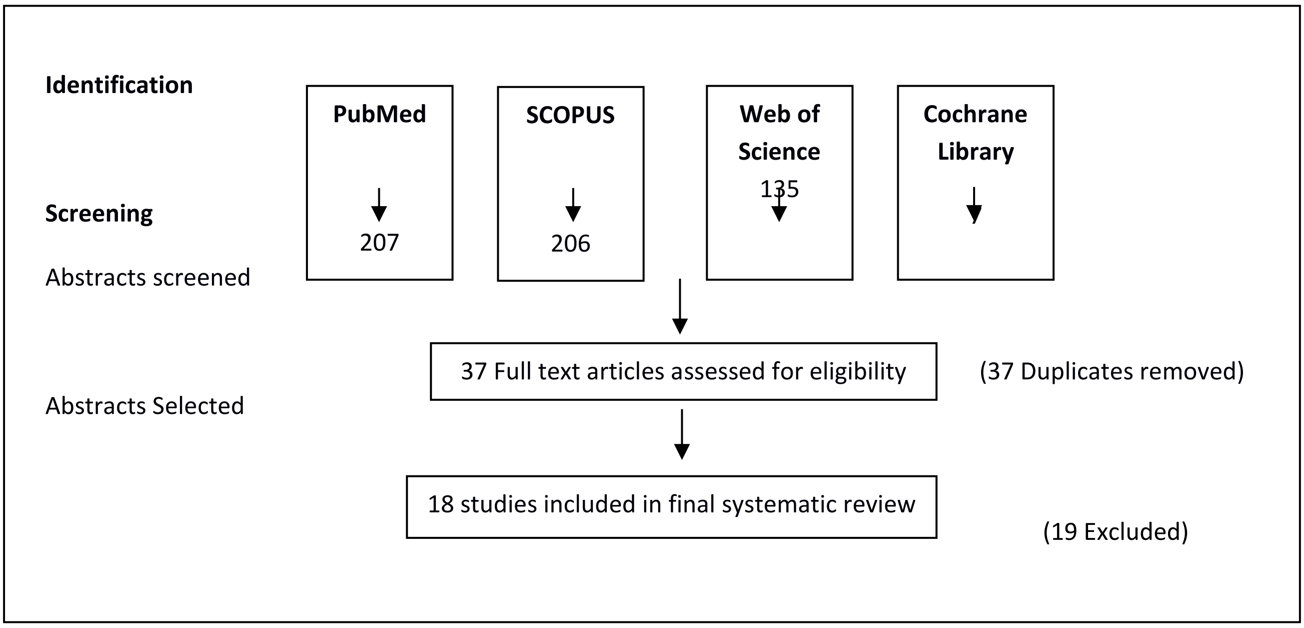
Identification
Screening
Abstracts screened
Abstracts Selected
PubMed
207
SCOPUS
206
Web of Science
135
Cochrane Library
37 Full text articles assessed for eligibility
(37 Duplicates removed)
18 studies included in final systematic review
(19 Excluded)

Figure 1.