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Family history of Alzheimer's disease limits improvement in cognitive function after bariatric surgery

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Abstract

Background/Objective: Bariatric surgery can reverse cognitive impairments associated with obesity. However, such benefits may be attenuated in individuals with a predisposing risk for cognitive impairment such as family history of Alzheimer's disease.

Methods: In all, 94 bariatric surgery participants completed a computerized cognitive test battery before and 12 weeks after surgery. Family history of Alzheimer's disease was obtained through self-report.

Results: In the overall sample, cognitive function improved in memory and attention/executive function 12 weeks post-surgery. Repeated measures showed similar rates of improvements in attention/executive function between patients with and without a family history of Alzheimer's disease. In contrast, only individuals without a family history of Alzheimer's disease exhibited post-operative improvements in memory. A family history of Alzheimer's disease was associated with greater post-surgery rates of cognitive impairment.

Conclusions: Family history of Alzheimer's disease may limit post-surgery cognitive benefits. Future studies should examine whether weight loss can modify the course of cognitive decline in patients at-risk for Alzheimer's disease.

Keywords

Obesity, bariatric surgery, cognitive function, Alzheimer's disease

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Introduction

A rapidly growing literature links obesity with increased risk for Alzheimer's disease (AD) and other forms of dementia.[1] Milder deficits in cognitive function are also found in obese individuals of all age groups[2] and the prevalence of cognitive dysfunction increases with rising levels of adiposity.[3] In fact, past work shows that approximately 23% of bariatric surgery candidates exhibit clinically meaningful levels of pre-operative impairments in memory,[4] suggesting that this severely obese cohort may be at greatest risk for AD.

Emerging evidence suggests the possibility that bariatric surgery may partially reverse obesity-related cognitive impairments. Supporting this notion is past work that shows bariatric surgery is associated with cognitive improvements 12 months following surgery and such gains may last up to 3 years later.[5,6] Nevertheless, it remains unclear whether bariatric surgery yields cognitive benefits among individuals at elevated risk for cognitive impairment. Although not yet examined, a family history of AD likely represents an important modifier of cognitive changes after bariatric surgery and numerous studies show that a family history of AD increases vulnerability to poor neurocognitive outcomes. Specifically, it is associated with increased risk for the disease,[7] accelerated cognitive decline,[8] and heightened sensitivity to AD-related brain changes (e.g. hippocampal atrophy, amyloid burden).[9–12]

Such findings raise the possibility that a family history of AD limits the cognitive benefits associated with bariatric

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Table 1. Demographic and clinical characteristics.

Variables	Overall Sample (N = 94)	Fhx AD (n = 14)	No Fhx AD (n = 80)	t/χ^2 statistic[a]	*p*
Baseline					
Age, mean (SD)	44.34 (11.15)	40.0 (11.42)	45.10 (10.99)	−1.59	0.12
Sex (% men)	16.0	21.4	15.0	0.37	0.55
Hypertension (%)	46.8	57.1	45.0	0.71	0.69
Diabetes (%)	26.6	28.6	26.3	0.03	0.76
Sleep apnea (%)	39.4	35.7	40.0	0.09	0.78
Fhx Parkinson's disease	3.2	7.1	2.5	0.83	0.36
Fhx vascular dementia	6.4	7.1	6.3	0.02	0.90

SD: standard deviation; Fhx: family history; AD: Alzheimer's disease.
[a]Statistical comparison is between the family history of AD groups.

surgery. The purpose of the current study was to examine cognitive function 12 weeks after bariatric surgery among patients with and without a family history of AD.

Methods

Participants

A total of 94 participants were recruited into a multi-site prospective study examining the neurocognitive effects of bariatric surgery. All bariatric surgery patients were part of the Longitudinal Assessment of Bariatric Surgery (LABS) parent project and were recruited from existing LABS sites (Columbia, Cornell, and Neuropsychiatric Research Institute).[13] Inclusion criteria included enrollment in LABS, between 20 and 70 years of age, and English-speaking. Exclusion criteria consisted of history of neurological disorder or injury (e.g. dementia, stroke, seizures), moderate or severe head injury (defined as >10 min loss of consciousness), past or current history of severe psychiatric illness (e.g. schizophrenia, bipolar disorder), past or current history of alcohol or drug abuse (defined by *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV) criteria), history of a learning disorder or developmental disability (defined by DSM-IV criteria), or impaired sensory function.

Within the sample, almost all patients underwent Roux-en-Y gastric bypass surgery (RYGB). Only one bariatric surgery patient underwent a gastric banding procedure, and thus, no comparisons for type of surgery were conducted. The current sample included bariatric surgery patients who had complete baseline demographic and medical data, and baseline and 12-week follow-up clinical (i.e. body mass index (BMI)) and cognitive data. Table 1 shows medical and demographic characteristics of the sample.

Predictors and outcomes

Family history of AD. Family history of AD was ascertained via participant self-report. A family history of AD demonstrates strong sensitivity and specificity in the identification of AD.[14] Family history of AD is believed to take into account both genetic (known and unknown) and non-genetic risk factors.[15] As such, a family history of AD is a sensitive and independent predictor of poor neurocognitive outcomes and AD-related neuropathological changes.[16,17]

Cognitive function. The IntegNeuro is a computerized cognitive test battery that was used to assess cognitive function. It taps into multiple cognitive domains, can be completed in 45–60 min, and demonstrates excellent psychometric properties.[18,19] Specifically, the IntegNeuro has been shown to exhibit good convergent and corresponding divergent validity with standardized paper and pencil neuropsychological tests.[18] Moreover, indices of the IntegNeuro also demonstrates excellent test–retest reliability (up to r = 0.89).[19] An alternate version of the IntegNeuro at the follow-up was also utilized to reduce practice effects. The cognitive domains and specific tests included the following.

Attention/executive function

Switching of attention. This task is a computerized adaptation of the Trail Making Test A and B.[20] Participants are first asked to touch a series of 25 numbers in ascending order as quickly as possible. This is followed by the presentation of 13 numbers (1–13) and 12 letters (A–L) that participants alternately touch in ascending order. These tests assess attention and psychomotor speed as well as executive function. Time to completion served as the outcome measure in the current study.

Maze task: This task is a computerized adaptation of the Austin Maze[21] and assesses executive function. Participants are presented with a grid (8 × 8 matrix) of circles and asked to identify the hidden path through the grid. Distinct auditory and visual cues are presented for correct and incorrect responses. The trial ends when the subject completed the maze twice without error or after 10 min have elapsed.

Memory

Verbal list-learning. Participants are read a list of 12 words a total of four times and asked to recall as many words as possible after each trial. Following presentation

and recall of a distraction list, participants are then asked to recall words from the original list. After a 20-min filled delay, participants are asked to freely recall the learned list and perform a recognition trial comprised of target words and non-target words. Total learning and long delayed free recall of these verbal list items assessed memory in the current study.

Language

Letter fluency. Participants are asked to generate words beginning with a given letter of the alphabet for 60 s. A different letter is used for each of the three trials. The total number of correct words generated across the three trials served as the dependent variable.

Animal fluency. In this task, participants generate as many animal names as possible in 60 s. Total correct served as the dependent variable.

Demographic and medical characteristics. Demographic and medical characteristics were ascertained via self-report and medical records. Medical records were reviewed by research staff to corroborate and supplement participant self-report.

Procedures

All procedures were approved by the Kent State University Institutional Review Board and all participants provided written informed consent prior to study involvement. All participants completed a computerized cognitive test battery at a pre-operative visit (within 30 days prior to surgery) and 12 weeks (± 7 days) post-operatively. Participants' height and weight were also measured at each time point and BMI was calculated using the standard formula. Participants also completed medical history self-report measures and a medical chart review was performed at these time points.

Statistical analysis

A series of analyses were conducted to determine whether bariatric surgery attenuates obesity-related risk for cognitive impairment and whether such benefits are limited by a family history of AD. Raw scores of all cognitive indices were transformed into T-scores (a distribution with a mean of 50 and a standard deviation (SD) of 10) using standardized normative data that take into account age, gender, and premorbid intelligence. A T-score < 35 was reflective of clinically meaningful impairment. This cutoff score represents 1.5 SD below the normative mean and is commonly used to characterize clinically meaningful impairments on cognitive test performance in clinical and research settings.[22,23] A mean composite score was computed at each time point for attention/executive function, memory, and language that consisted of the T-scores of the respective neuropsychological measures that comprise each domain. Independent sample t-tests and chi-square analyses were performed to examine differences in age and medical status between bariatric surgery patients with and without a family history of AD.

Repeated measures analysis of variance (ANOVA) examined changes in BMI, attention/executive function, memory, and language from baseline to 12 weeks after surgery. At each time point, chi-square analyses examined rates of impairments on the cognitive tasks between patients with and without a family history of AD. Family history of AD (yes or no) was then entered as a grouping variable in the repeated measures models examining cognitive function over time to determine between-group differences in post-operative cognitive changes. For these analyses, sex and change in BMI served as covariates; change in BMI consisted of a difference score between baseline and 12-week BMI. Sex and BMI were included as covariates because of their well-known effects on post-bariatric surgery outcomes.[2,24] Age was not entered as a covariate, as a recent study shows that age does not influence post-surgery cognitive outcomes.[25] To capture the unique genetic variance of a family history of AD, we also controlled for a family history of other neurodegenerative disease that increase susceptibility to cognitive impairment during older age, including a family history of Parkinson's disease and vascular dementia. Indeed, family history of Parkinson's disease as well as neurodegenerative diseases more broadly is a significant risk factor for dementia, including AD.[26,27]

Results

Medical and clinical characteristics

The sample fell in the severely obese classification at baseline with an average BMI of 45.94 (SD = 5.27) kg/m^2. Although the sample remained in the severely obese range at the 12-week follow-up (mean (SD) = 38.03 (4.92)), a significant decline in BMI was still noted ($F(1, 93) = 1010.65$, $p < 0.001$). At baseline, diagnostic status of hypertension (46.8%), diabetes (26.6%), and sleep apnea (39.4%) was prevalent. Few participants had a family history of Parkinson's disease (3.2%) and vascular dementia (6.4%; see Table 1).

Of the sample, 14.9% reported a family history of AD. Independent samples t-tests showed no significant age differences between bariatric surgery patients with and without a family history of AD ($t(92) = -1.59$, $p = 0.12$). Likewise, chi-square analyses revealed no between-group differences for sex ($\chi^2(N = 94, df = 1) = 0.37$, $p = 0.55$), hypertension ($\chi^2(N = 94, df = 1) = 0.75$, $p = 0.69$), diabetes ($\chi^2(N = 94, df = 1) = 0.55$, $p = 0.76$), sleep apnea ($\chi^2(N = 94, df = 1) = 0.50$, $p = 0.78$), or family history of Parkinson's disease ($\chi^2(N = 94, df = 1) = 0.83$, $p = 0.36$), and vascular dementia ($\chi^2(N = 94, df = 1) = 0.02$, $p = 0.90$). See Table 1 for between-group differences in medical and demographic characteristics. Repeated-measure ANOVA also showed no between-group differences between bariatric surgery patients with and without a family history of AD on pre- to post-operative BMI

Table 2. Post-operative changes in BMI.

Group	Baseline BMI, M (SD)	12-week BMI, M (SD)	F-statistic for time
Fhx AD (n = 14)	45.17 (5.02)	37.85 (5.43)	900.03**
No Fhx AD (n = 80)	46.07 (5.33)	38.06 (4.86)	115.03**

SD: standard deviation; BMI: body mass index; Fhx: family history; AD: Alzheimer's disease.
There was no significant Group × Time effect ($p > 0.05$).
**$p < 0.001$

Table 3. Baseline and 12-week cognitive test descriptives in the full sample (N = 94).

Neuropsychological domains tests	Baseline,M (SD)	% T-score < 35	12-week, M (SD)	% T-score < 35	F-statistic (p)
Attention/executive function	52.47 (11.85)	9.6	57.39 (10.01)	3.2	39.26 (<0.001)
SOA-A	54.93 (14.62)	10.6	58.60 (13.57)	5.3	8.13 (0.01)
SOA-B	52.90 (14.92)	6.4	58.47 (11.55)	4.3	23.04 (<0.001)
Maze errors	49.59 (13.54)	12.8	55.13 (11.97)	6.4	24.88 (<0.001)
Memory	44.39 (10.68)	18.1	47.71 (12.36)	12.1	9.77 (<0.01)
Learning	43.17 (12.40)	23.4	46.49 (13.81)	17.0	7.33 (0.01)
LDFR	45.62 (10.68)	12.8	48.94 (12.97)	16.0	7.93 (0.01)
Language	48.61 (9.30)	5.3	48.87 (8.68)	4.3	0.16 (0.69)
Verbal fluency	46.85 (11.34)	17.0	47.31 (10.58)	13.8	0.37 (0.54)
Animals	50.38 (10.28)	3.2	50.42 (10.25)	4.3	0.00 (0.96

SD: standard deviation; SOA: switching of attention; LDFR: long delay free recall.
Test scores are reported as T-Scores.

changes (Group × Time effect: $F(1, 92) = 0.94$, $p = 0.33$), see Table 2. There were also no between-group cross-sectional differences in BMI at each time point (baseline: $t(92) = -0.59$, $p = 0.56$; 12 weeks: $t(92) = -0.15$, $p = 0.88$).

Bariatric surgery and cognitive function

Table 3 presents baseline and post-surgery cognitive test performance in the overall sample. Many participants exhibited meaningful levels of cognitive impairment (i.e. T score < 35) at baseline, most commonly in learning (23.4%) and letter fluency (17.0%). As shown in Table 3, at the 12-week follow-up, cognitive impairment became less prevalent on nearly all measures. Likewise, repeated measures ANOVA showed a significant main effect in attention/executive function ($F(1, 93) = 39.26$, $p < 0.001$) and memory ($F(1, 93) = 9.77$, $p < 0.01$) from baseline to 12 weeks post-operatively in the overall sample. For both domains, cognitive test performance improved over time. No such pattern emerged for language abilities ($F(1, 93) = 0.16$, $p = 0.69$).

Family history of AD and post-operative cognitive changes

Chi-square analyses revealed that bariatric surgery patients with a family history of AD were no more likely to exhibit impairments on any of the cognitive measures ($p > 0.10$ for all) at baseline, see Table 4. Similarly, at baseline, ANOVA analyses controlling for sex, change in BMI, and family history of Parkinson's disease and vascular dementia showed no differences in attention/executive ($F(1, 88) = 0.15$, $p = 0.70$), memory ($F(1, 88) = 0.004$, $p = 0.95$), or language ($F(1, 88) = 2.13$, $p = 0.15$) between those patients with and without a family history of AD.

Repeated-measures ANOVA controlling for sex, BMI change, and a family history of Parkinson's disease and vascular dementia showed a significant family history of AD × time effect for memory (Group × Time: $F(1, 88) = 4.09$, $p = 0.046$). Follow-up repeated measures showed that memory abilities remained relatively stable in bariatric surgery patients with a family history of AD ($F(1, 9) = 0.16$, $p = 0.70$), while patients without such history exhibited significant improvements ($F(1, 75) = 5.03$, $p = 0.03$). There were no significant between group differences for attention/executive function (Group × Time = ($F(1, 88) = 0.52$, $p = 0.47$). However, unadjusted follow-up repeated measures showed only patients without a family history of AD exhibited significant improvements in attention/executive function ($F(1, 79) = 36.02$, $p < 0.001$). Refer to Table 5.

Interestingly, bariatric surgery patients without a family history of AD exhibited fewer impairments on many of the individual cognitive tasks at the 12-week time point. In contrast, those patients with such history actually exhibited greater impaired performances post-operatively relative to baseline (see Table 4). Indeed, bariatric surgery patients with a family history of AD were more likely to exhibit

Table 4. Family history of Alzheimer's disease and rates of pre- and post-operative cognitive impairment.

	Baseline % T-score < 35			12-week % T-score < 35		
	Fhx AD	No Fhx AD	Chi-square	Fhx AD	No Fhx AD	Chi-square
Attention/executive function						
SOA-A	7.1	11.3	0.21	21.4	2.5	8.48*
SOA-B	0.0	7.5	1.12	0.0	5.0	0.73
Maze errors	21.4	11.3	1.11	0.0	7.5	1.12
Memory						
Learning	35.7	21.3	1.39	28.6	15.0	1.55
LDFR	21.4	11.3	1.11	35.7	12.5	4.79*
Language						
Verbal fluency	28.6	15.0	1.55	35.7	10.0	6.61*
Animals	7.1	2.5	0.83	14.3	2.5	4.06*

SD: standard deviation; SOA: switching of attention; LDFR: long delay free recall; Fhx: family history; AD: Alzheimer's disease.
*$p < 0.05$

Table 5. Cognitive changes 12 weeks following bariatric surgery for patients with and without a history of AD.

	Fhx AD (n = 14)		No Fhx AD (n = 80)		Group × Time
	Baseline	12 weeks	Baseline	12 weeks	
Attention/EF	53.61 (11.36)	56.98 (9.01)	52.28 (11.99)	57.47 (10.23)	0.52
Memory	43.40 (11.38)	42.41 (14.17)	44.57 (10.62)	48.68 (11.85)	4.09*
Language	45.05 (9.74)	45.75 (12.07)	49.24 (9.15)	49.41 (7.92)	0.20

EF: executive function; Fhx: family history; AD: Alzheimer's disease; BMI: body mass index.
Analyses controlled for sex, BMI change, and family history of Parkinson's disease and vascular dementia.
**$p < 0.001$.

impairments on the long delay free recall task ($\chi^2(N = 94, df = 1) = 4.79$, $p = 0.03$), switching of attention task A ($\chi^2(N = 94, df = 1) = 8.48$, $p = 0.004$), letter fluency ($\chi^2(N = 94, df = 1) = 6.61$, $p = 0.01$), and animal fluency ($\chi^2(N = 94, df = 1) = 4.06$, $p = 0.04$) 12 weeks after surgery.

Discussion

Obesity is a risk factor for cognitive impairment and adverse neurological changes, including AD. Consistent with past work, bariatric surgery improved cognitive function in a sample of severely obese persons. However, the current study extends the literature by showing that a family history of AD may limit the post-operative cognitive gains in this high-risk population. Several aspects of these findings warrant further discussion.

In the current study, bariatric surgery patients with a reported family history of AD exhibited a higher prevalence of cognitive impairment and did not show post-operative gains in memory abilities. Family history of AD increases vulnerability for a range of adverse neurocognitive outcomes, including accelerated cognitive decline[8] and increased risk for AD.[7] Indeed, the lack of improvements in memory among patients with a family history of AD is noteworthy given the implications of this domain in AD pathogenesis. Although not entirely clear, the mechanisms for these findings likely involve the association of a family history of AD with preclinical AD-related structural and functional brain changes, particularly among regions that mediate memory abilities. For example, a family history of AD is associated with AD pathology (i.e. increased amyloid burden),[7,28] global and hippocampal atrophy,[12,17,29] and reduced activation of mesial temporal lobe structures.[16,30] Alternatively, a family history of AD may also limit post-operative cognitive benefits via indirect mechanisms such as heightened risk for cardiovascular disease. As an example, apolipoprotein E-4 (APOE-4) has been shown to exacerbate the negative effects of cardiovascular disease and its risk factors (e.g. hypertension) on cognitive function.[31] Clearly, prospective studies that employ advanced neuroimaging are much needed to elucidate the effects of a family history of AD on the brain in bariatric surgery patients.

In the overall sample, we found that bariatric surgery was associated with improvements in both attention/executive function and memory abilities 12 weeks post-operatively. Growing attention has been paid to the possible neuroprotective effects of bariatric surgery in obese individuals,[2] and recent work shows that the substantial weight loss following

bariatric surgery associated with improved cognitive function up to 3 years post-operatively.[6] The mechanisms for these cognitive benefits are not well understood and likely multifactorial. Bariatric surgery produces many physiological changes with the potential to benefit cognitive function, including resolution of comorbid medical conditions (e.g. diabetes),[32] stabilization of appetitive hormones (i.e. leptin and ghrelin),[33,34] and decreased inflammation.[35] Such physiological changes are known to acutely improve cognitive function[36–38] and may also attenuate the known pattern of accelerated cognitive decline in obese persons.[39] However, it appears that such changes are not sufficient to improve memory function in surgical patients with a family history of AD, raising the possibility that such persons may already have preclinical AD changes.[12,17,29] Some evidence for this possibility may already exist, as obese persons have been shown to exhibit AD-related neuropathology such as higher levels of amyloid beta, tau, and amyloid precursor protein.[35,40] It still remains possible that bariatric surgery may modify the course of rapid cognitive decline or neurodegenerative conditions in patients with a family history of AD, although this awaits empirical test with prospective studies that implement extended follow-ups (i.e. 10 years).

Findings from the current study are limited in several ways. First, the nature of recruitment for the current study did not target individuals at risk for AD, and larger samples of bariatric surgery patients are much needed to elucidate the effects of a family history of AD on post-operative cognitive changes. This study did not perform genetic testing, and thus, no information on APOE genotype was available. Although genetic testing presents with certain barriers such as high expense, the lack of APOE status is an important limitation and future studies that employ genetic testing in bariatric surgery patients would help clarify the observed findings. For example, family history of AD and APOE-4 has been shown to co-occur in as many as 45% of adult offspring of AD patients.[41] These genetic AD-risk factors interact[12] and also introduce unique mechanisms by which they impact the brain and cognitive function. In addition, the young age of the current sample (mean age = 44) may have limited variability in rates of cognitive impairment. Future studies that examine the impact of bariatric surgery among older adult patients more vulnerable to neurological impairment (e.g. 55–70 years old) are needed to determine whether surgical intervention can reduce risk for accelerated age-related cognitive decline and/or AD in severely obese individuals with and without a family history of AD. Lastly, practice effects should always be considered when examining cognitive test performance over time. However, practice effects in this study likely do not represent a significant concern given past work that documents cognitive improvements in bariatric surgery patients relative to obese controls[6] and because we examined the impact of a family history of AD using two patient groups: those with and without a genetic history of AD. Similar to this notion, an alternate form of the IntegNeuro was utilized and practice effects on computerized cognitive test batteries are minimal.[42] Regardless, future studies that implement a healthy obese control group with and without a genetic history of AD and administer a more comprehensive cognitive test battery are needed to confirm the impact of a family history of AD on post-surgery cognitive outcomes.

In brief summary, the current study suggests that a family history of AD limits the acute cognitive benefits associated with bariatric surgery. Prospective studies with long-term follow-ups that employ neuroimaging are needed to clarify mechanisms and determine whether weight loss surgery can still alter the course of cognitive decline or AD progression in bariatric surgery patients at-risk for AD.

Declaration of conflicting interests

The authors disclose no conflict of interest.

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