Original Research

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The Effect of Surgical Weight Loss on Cognition in Individuals with Class II/ III Obesity

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Abstract

BACKGROUND: Obesity is a global epidemic and is associated with cognitive impairment and dementia. It remains unknown whether weight loss interventions, such as bariatric surgery, can mitigate cognitive impairment.

OBJECTIVES: We aimed to determine the effect of surgical weight loss on cognition in individuals with class II/III obesity.

DESIGN: We performed a prospective cohort study of participants who underwent bariatric surgery. At baseline and two years following surgery, participants completed metabolic risk factor and neuropsychological assessments.

SETTING: Participants were enrolled from an academic suburban bariatric surgery clinic.

PARTICIPANTS: There were 113 participants who completed baseline assessments and 87 completed two-year follow-up assessments (66 in-person and 21 virtual) after bariatric surgery. The mean (SD) age was 46.8 (12.5) years and 64 (73.6%) were female.

INTERVENTION: Bariatric surgery. There were 77 (88.5%) participants that underwent sleeve gastrectomy and 10 (11.5%) that underwent gastric bypass surgery.

MEASUREMENTS: Cognition was assessed using the NIH toolbox cognitive battery (NIHTB-CB) and the Rey Auditory Verbal Learning Test (AVLT). The primary outcome was the change in NIHTB-CB fluid composite score before and after surgery.

RESULTS: The primary outcome, NIHTB-CB composite score, was stable following bariatric surgery (-0.4 (13.9), p=0.81,n=66). Among secondary outcomes, the NIHTB-CB dimensional card sorting test (executive function assessment), improved (+6.5 (19.9),p=0.01,n=66) while the Rey AVLT delayed recall test (memory assessment) declined (-0.24 (0.83),p=0.01,n=87) following surgery. Improvements to metabolic risk factors and diabetes complications were not associated with improvements to NIHTB-CB composite score. The other 4 NIHTB-CB subtests and Rey AVLT assessments of auditory learning and recognition were stable at follow-up.

CONCLUSIONS: Following bariatric surgery, the age-adjusted composite cognitive outcome did not change, but an executive subtest score improved. These results suggest that bariatric surgery may mitigate the natural history of cognitive decline in individuals with obesity, which is expected to be faster than normal aging, but confirmatory randomized controlled trials are needed. The decline in delayed recall also warrants further studies to determine potential differential effects on cognitive subtests.

Key words: Cognition, bariatric surgery, obesity, type 2 diabetes, diabetes complications.

Introduction

Obesity is an epidemic that, by 2030, is projected to affect nearly 50% of adults in the United States (US) (1). Along with the burden of managing the primary condition, obesity is associated with various comorbid complications, including cognitive impairment. The 2020 Lancet Commission on dementia prevention, intervention, and care concluded that obesity was a modifiable risk factor for dementia (2). Along similar lines, a 2020 meta-analysis found that midlife obesity increases the risk of cognitive impairment and dementia (3). Our recent study of adults with class II/ III obesity found that increased central obesity measurements were associated with reduced cognitive function (4). We also found that central obesity was the most important risk factor for executive function ability, even after taking into account demographic information, numerous psychiatric and medical comorbidities, medication use, and the presence of obstructive sleep apnea (5). In addition to obesity, recent meta-analyses found that type 2 diabetes is associated with an increased likelihood of cognitive impairment and dementia, and the metabolic syndrome is associated with vascular dementia and progression from mild cognitive impairment to dementia, but not with incident dementia or Alzheimer's Disease (6, 7). Furthermore, midlife obesity and type 2 diabetes may accelerate the rate of cognitive decline (8). Finally, our study of over 1.2 million individuals found that having diabetes complications, such as neuropathy or chronic kidney disease (CKD), significantly increased the likelihood of having a cognitive disorder (9).

Given the frequent comorbidity of obesity, type 2 diabetes, metabolic syndrome, and diabetes complications, and their established risk for cognitive decline, interventions that simultaneously target these risk factors are needed, such as surgical weight loss. Indeed, a recent meta-analysis (20 studies, 8 unique cohorts) found bariatric surgery improved cognitive function, particularly aspects of memory, suggesting that surgical weight loss might effectively impede cognitive decline (10). However, the previous studies had limitations, including small sample sizes, short follow-up periods, primary focus on gastric bypass surgery, limited metabolic risk factor phenotyping, and/or absence of comprehensive neuropsychological testing. Therefore, a higher class of

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evidence is needed to determine whether bariatric surgery stabilizes or improves sensitive measures of a broad spectrum of cognitive domains and especially over longer-term follow-up. Indeed, the 2020 Lancet Commission concluded that "data about the long-term effects or the effect of weight loss in preventing dementia are absent" (2).

To address this critical gap in knowledge, we assessed the effects of bariatric surgery on cognition in a US population with class II/III obesity based on a neuropsychological examination following longer-term 2-year follow up. We examined the effects of sleeve gastrectomy on cognition changes, given it is now the most common bariatric surgery procedure (11, 12). Moreover, additional evidence is needed to determine whether specific improvements to obesity, type 2 diabetes, metabolic syndrome, or diabetes complications are differentially associated with cognitive changes. Thus, we also assessed how changes in obesity, type 2 diabetes, other metabolic risk factors, and diabetes complications were associated with cognitive changes following bariatric surgery.

Methods

Study population

From April 2015 to May 2018, participants with class II/III obesity were enrolled from the University of Michigan bariatric surgery clinic. Inclusion and exclusion criteria were previously described4. At baseline, prior to bariatric surgery, and 2 years following bariatric surgery, participants underwent metabolic phenotyping, diabetes complication assessments, and a neuropsychological screening examination. Due to the COVID-19 pandemic, some participants completed 2-year follow-up assessments virtually over video conference.

Metabolic phenotyping, anthropometric measurements, intelligence quotient, psychiatric conditions, and other medical comorbidities

Participants had the following collected: fasting lipid panel, glycated hemoglobin (HbA1c), blood pressure, height, weight, body mass index (BMI), and anthropometric measurements. Anthropometric measurements were assessed at 9 separate locations (arm, forearm, calf, mid-thigh, hips/thighs, abdomen, buttocks/hips, low-waist, high-waist), as previously described (13). Participants without diabetes also underwent 2-hour glucose tolerance testing. After completing bariatric surgery, many participants could not tolerate glucose tolerance testing; therefore, these data were not collected after June 2018. At baseline, we determined diabetes status using HbA1c and glucose tolerance testing measurements, according to 2022 American Diabetes Association Standards of Care. Participants completing virtual follow-up only had height, weight, BMI, and anthropometric measurements.

Participant intelligence quotient (IQ) was measured using either the Shipley-2 and/or Wechsler Abbreviated Scale Intelligence 2nd Edition (mean=100, standard deviation (SD)=15). The Wide Range Achievement Test 4 (WRAT-4) evaluated participant baseline academic skills in reading and math (mean=100, SD=15). The Minnesota Multiphasic Personality Inventory 2- Restructured Form (MMPI-2RF) Clinical (RC) assessed somatic complaints (RC1), low positive emotions (RC2), and anxiety (RC7) at baseline. Each MMPI scale was standardized to mean=50 and SD=10.

Diabetes complications (continuous measures)

Peripheral neuropathy was evaluated using intraepidermal nerve fiber density (IENFD, unit=fibers/mm) measured at the distal leg and proximal thigh (14). Cardiovascular autonomic neuropathy (CAN) was evaluated using the expiration/inspiration (E/I) ratio, one of the five Ewing cardiovascular reflex tests, that are the gold standard for autonomic testing (15, 16). Retinopathy was evaluated using the mean deviation as calculated using frequency doubling technology (FDT) testing with the 24-2 program (17). CKD was evaluated using the estimated glomerular filtration rate (eGFR, unit=mL/min/1.73 m^2), calculated using the 2021 CKD Epidemiology Collaboration equatio (18). Participants completing virtual follow-up did not have diabetes complications measurements.

At baseline, we determined the prevalence of diabetes complications using the Toronto consensus definition of probable neuropathy for PN (19), the 5th percentile of E/I ratio values from a previously described control population without obesity (E/I ratio<1.09) for CAN4, diagnosis of any retinopathy based on ophthalmologist review of nonmydriatic retinal photographs, and the Kidney Disease: Improving Global Outcomes criteria as having eGFR<60mL/min/1.73m^2 or albumin-to-creatinine ratio≥30mg/g for CKD.

Cognition

The primary outcome was the change in the NIH Toolbox Cognition Battery (NIHTB-CB) fluid composite score. The NIHTB-CB fluid composite score aggregates across the flanker inhibitory control and attention test (attention and executive function), picture sequence memory test (episodic memory), list sorting test (working memory), pattern comparison test (processing speed), and dimensional change card sort test (executive function). Secondary outcomes included the five individual NIHTB-CB tests. All NIHTB-CB outcomes were standardized based on participant age (mean=100, SD=15). Other secondary outcomes included the Rey Auditory Verbal Learning Test (AVLT) assessment of auditory learning, delayed recall, and recognition. The AVLT is a verbal list learning task that requires participants to learn a list of words over repeated presentation (auditory learning task) and then accurately recall these words after a lengthy delay (delayed recall task) (20, 21). Following the delayed recall task, participants are presented with a recognition paradigm, where they are tasked with identifying the original list of words among a list also containing semantically or phonemically similar words (recognition task).

Table 1. Baseline demographic information of study participants and those lost to follow-up

Characteristic	All participants, n=113	Completed follow-up in-person n=66	Lost to in-person follow-up, n=47	P-value	Completed follow-up in-person or virtual, n=87	Lost to in-person or virtual follow-up, n=26	P-value
Age, mean (SD)	45.8 (12.6)	46.6 (13.0)	44.8 (12.1)	0.50	46.8 (12.5)	41.5 (12.6)	0.07
Sex, n(%) Female	86 (76.1)	47 (71.2)	39 (83.0)	0.18	64 (73.6)	22 (84.6)	0.30
Race, n(%)				>0.99			0.58
White	88 (77.9)	52 (78.8)	36 (76.6)		67 (77.0)	21 (80.8)	
Black	19 (16.8)	11 (16.7)	8 (17.0)		16 (18.4)	3 (11.5)	
Multi Racial	4 (3.5)	2 (3.0)	2 (4.3)		3 (3.4)	1 (3.8)	
Other	2 (1.8)	1 (1.5)	1 (2.1)		1 (1.1)	1 (3.8)	
Ethnicity, n(%) Hispanic/Latino	1 (0.9)	1 (1.5)	0 (0.0)	>0.99	1 (1.1)	0 (0.0)	
Smoking Status, n(%)				>0.99			>0.99
Never Smoker	79 (69.9)	46 (69.7)	33 (70.2)		60 (69.0)	19 (73.1)	0.81
Ex-Smoker	34 (30.1)	20 (30.3)	14 (29.8)		27 (31.0)	7 (26.9)	
Marital Status, n(%)				0.81			0.56
Married	63 (55.8)	39 (59.1)	24 (51.1)		51 (58.6)	12 (46.2)	
Single	30 (26.5)	15 (22.7)	15 (31.9)		21 (24.1)	9 (34.6)	
Divorced	16 (14.2)	10 (15.2)	6 (12.8)		11 (12.6)	5 (19.2)	
Widowed	2 (1.8)	1 (1.5)	1 (2.1)		2 (2.3)	0 (0.0)	
Significant Other	2 (1.8)	1 (1.5)	1 (2.1)		2 (2.3)	0 (0.0)	
Education, n(%)				0.88			0.96
College Degree	47 (41.6)	28 (42.4)	19 (40.4)		36 (41.4)	11 (42.3)	
Some College or Vocational College	37 (32.7)	22 (33.3)	15 (31.9)		28 (32.3)	9 (34.6)	
Professional or Graduate Degree	17 (15.0)	8 (12.1)	9 (19.1)		14 (16.1)	3 (11.5)	
High School Graduate or GED	11 (9.7)	7 (10.6)	4 (8.5)		8 (9.2)	3 (11.5)	
High School or less	1 (0.9)	1 (1.5)	0 (0.0)		1 (1.1)	0 (0.0)	
Employment Status, n(%)				0.40			0.64
Employed	76 (67.3)	43 (65.2)	33 (70.2)		57 (65.5)	19 (73.1)	
Retired	12 (10.6)	7 (10.6)	5 (10.6)		10 (11.5)	2 (7.7)	
Keeping House	9 (8.0)	5 (7.6)	4 (8.5)		7 (8.0)	2 (7.7)	
Student	4 (3.5)	1 (1.5)	3 (6.4)		2 (2.3)	2 (7.7)	
Seeking Work	1 (0.9)	1 (1.5)	0 (0.0)		1 (1.1)	0 (0.0)	
Other	11 (9.7)	9 (13.6)	2 (4.3)		10 (11.5)	1 (3.8)	
Insurance, n(%)				0.80			0.79
Private	81 (71.7)	47 (71.2)	34 (72.3)		60 (69.0)	21 (80.8)	
Multiple	17 (15.0)	10 (15.2)	7 (14.9)		13 (14.9)	4 (15.4)	
Medicaid	8 (7.1)	5 (7.6)	3 (6.4)		7 (8.0)	1 (3.8)	
Medicare	2 (1.8)	2 (3.0)	3 (6.4)		2 (2.3)	0 (0.0)	
Other	5 (4.4)	2 (3.0)	0 (0.0)		5 (5.7)	0 (0.0)	
IQ	102.6 (11.2)	103.0 (11.8)	102.1 (10.3)	0.69	102.9 (10.8)	101.8 (12.3)	0.68
WRAT-4	96.4 (10.4)	96.2 (8.1)	96.6 (12.9)	0.84	96.5 (9.1)	96.1 (14.0)	0.89
MMPI							
MMPI RC1	52.1 (13.5)	51.2 (15.1)	53.3 (10.8)	0.38	53.2 (10.5)	54.4 (10.7)	0.60
MMPI RC2	49.4 (13.4)	49.5 (15.8)	49.3 (9.0)	0.95	51.3 (11.3)	49.2 (8.3)	0.32
MMPI RC7	45.4 (12.6)	45.0 (14.6)	45.9 (9.5)	0.68	46.7 (10.6)	46.3 (9.6)	0.88

P-values for continuous variables were calculated using a two-sample t-test. P-values for categorical variables were calculated using Fisher's exact test. IQ, intelligence quotient; WRAT-4, Wide Range Achievement Test 4; MMPI, Minnesota Multiphasic Personality Inventory; MMPI RC1, MMPI Restructured Clinical scales of somatic complaints; MMPI RC2, MMPI RC of positive emotions; MMPI RC7, MMPI RC of anxiety.

NIHTB-CB assessments were performed with participants that completed in-person follow-up visits. Rey AVLT assessments were performed with participants that completed follow-up in-person prior to COVID-19 and virtually after COVID-19.

Statistical analysis

Outcomes and analyses were specified a priori. The primary outcome was the change in NIHTB-CB composite score after bariatric surgery. The primary analysis was to determine the change in NIHTB-CB composite score after bariatric surgery. Other outcomes and analyses were secondary. Within-participant changes to continuous variables were calculated by subtracting baseline from follow-up measures.

Descriptive statistics summarized participant demographic information, metabolic phenotyping, diabetes complications, and study outcomes at baseline and two years following bariatric surgery. Independent two-sample t-tests (for continuous variables) and Pearson's Chi-Square test (for categorical variables) compared demographic information between participants that did versus that did not complete in-person follow-up, and between participants that did versus that did not complete virtual or in-person follow-up. Paired t-tests compared within-participant differences in continuous cognitive assessments at follow-up.

Multivariable linear regression models were fit to determine the association between changes in primary (NIHTB-CB composite score) and secondary (Rey AVLT delayed recall) cognition outcomes with changes in metabolic risk factors and diabetes complication separately, after adjusting for age, sex, and baseline BMI, WRAT4, and outcome measurements.

Available case analysis handled missing data. Analyses were completed using R version 4.0.2.

Results

Study participation and missing data

Of the 163 individuals who consented to participate in the study, 113 (69.3%) completed baseline neuropsychological screening evaluations and bariatric surgery. Sixty-six participants (58.4%) completed in-person 2-year follow-up visits, and an additional twenty-one participants (18.6%) completed partial virtual measures due to COVID-19 (total of 77.0% with follow-up). Reasons for withdrawing included not wanting electromyography or skin biopsy (n=1), family health issues (n=1), scheduling conflicts (n=2), moved out of state (n=1), medical reasons (n=1), deceased (n=1), and loss to follow-up (n=19).

There were no demographics differences in participants that completed in-person follow-up, completed virtual follow-up, and were lost to follow-up (Table 1, all p>0.05). Of the 87 participants who completed follow-up, 77 (88.5%) underwent sleeve gastrectomy and 10 (11.5%) underwent gastric bypass surgery.

Several participants had sporadic missing information at baseline (V1) and follow-up (V2). Participants with in-person follow-up (n=66) had missing data for: buttocks/hips circumference (V2: 1), low-density lipoprotein (V2: 1), HbA1C (V1: 1), IENFD of the distal leg (V1: 2, V2: 3), IENFD of the proximal thigh (V1: 1, V2: 1), E/I ratio (V2: 7), mean deviation on FDT testing (V2: 1), WRAT-4 (V1: 3, V2: 3), NIHTB-CB (V2: 3), and Rey AVLT (V2: 2). Participants with virtual follow-up also had missing data for: weight (V2: 2), low-waist (V2: 2), arm (V2: 2), forearm (V2: 2), calf (V1: 2), mid-thigh (V2: 2), hips/thighs (V2: 2), abdomen (V2: 2), buttocks/hips (V2: 2), and high-waist circumferences (V2: 2), Rey AVLT total auditory learning (V2: 3), delayed recall (V2: 3), and recognition (V2: 2). Diabetes complications (IENFD, E/I ratio, mean deviation on FDT testing, eGFR) and some metabolic risk factors (systolic blood pressure, fasting glucose, high-density lipoprotein, triglycerides, HbA1c) were not measured at virtual follow-up assessments.

Demographic information, baseline neuropsychological evaluation, change in metabolic risk factors, and change in diabetes complications

Of participants who completed in-person or virtual follow-up (n=87), the mean (SD) age was 46.8 years (12.5), most were White (77.0%), and non-Hispanic (98.9%). Fourteen (16.1%) participants had a graduate degree, 36 (41.4%) had a college degree, 28 (32.2%) had some college experience, 8 (9.2%) had a high school degree, and 1 (1.1%) had less than a high school education. The mean (SD) IQ was average (102.9 (10.8)) as were reading skills (WRAT-4, 96.5 (9.1)). Assessments of somatic complaints (RC1, 53.2 (10.5)), low positive emotions (RC2, 51.3 (11.3)), and anxiety (RC7, 46.7 (10.6)) were all within normal ranges.

For the 87 participants that completed 2-year follow-up assessments, at baseline the mean (SD) BMI was 46.4 kg/m^2 (7.1), waist circumference was 134.6 cm (7.1), SBP was 129.4 mmHg (14.5), triglycerides were 125.6 mg/dL (66.6), HDL was 44.9 mg/dL (12.1), and HbA1c was 6.1% (1.0). In addition, we found 24 (27.6%) participants had diabetes and 25 (28.7%) were receiving anti-hyperglycemic medications. Finally, 19 (21.8%) participants had PN, 19 (21.8%) had CAN, 2 (2.3%) had retinopathy, and 2 (2.3%) had CKD. As previously published, all metabolic risk factors improved following bariatric surgery, except for blood pressure and total cholesterol22. In addition, IENFD at the proximal thigh improved, whereas IENFD at the distal leg, CAN, and retinopathy were stable, and CKD slightly worsened (22).

Change in cognition (Table 2)

The mean (SD) NIHTB-CB was above average at baseline (106.0 (16.2)) and two years following bariatric surgery (106.7 (16.1)). The primary cognition measure (NIHTB-CB composite score) was stable after bariatric surgery (-0.4

Table 2. Changes in cognition following bariatric surgery

Variable	Baseline Mean (SD)	2 Year Follow-up Mean (SD)	Change Mean (SD)	P-value (Paired T-Test)
NIH Toolbox Cognition Battery				
Fluid Cognition Composite (n=66)	106.0 (16.2)	106.7 (16.1)	-0.4 (13.9)	0.81
Visual Flanker (n=66)	95.1 (17.3)	95.5 (11.5)	0.0 (19.2)	>0.99
Dimensional Change Card Sort (n=66)	104.7 (20.2)	111.9 (17.8)	6.5 (19.9)	0.01
Pattern Comparison Processing Speed (n=66)	103.2 (23.6)	102.0 (17.4)	-2.3 (20.5)	0.38
Picture Sequence Memory (n=66)	105.3 (21.9)	110.2 (19.3)	4.3 (19.8)	0.09
List Sorting (n=66)	103.1 (18.0)	103.8 (14.0)	0.3 (16.5)	0.90
Rey AVLT				
Auditory Learning (n=87)	0.16 (0.91)	0.02 (0.95)	-0.15 (1.0)	0.20
Delayed Recall (n=87)	0.04 (0.93)	-0.21 (0.96)	-0.24 (0.83)	0.01
Recognition (n=87)	1.02 (0.71)	1.0 (0.70)	-0.01 (0.67)	0.93

P-values were calculated using paired t-tests. NIH Toolbox variables reported are standardized by age. Rey AVLT, Rey Auditory Verbal Learning Test.

(13.9), p=0.81). One NIHTB-CB executive function subtest, dimensional card sorting task, significantly improved at follow-up (+6.5 (19.9), p=0.01). The other 4 NIHTB-CB subtests were stable at follow-up. In contrast, the Rey AVLT assessment of participants' delayed recall memory significantly declined following bariatric surgery (-0.24 (0.83), p=0.01). The Rey AVLT assessment of auditory learning and recognition were stable at follow-up.

Association between metabolic risk factors and cognition (Table 3)

No improvement to any metabolic risk factor was associated with improvement in cognition. However, we found that significant decreases in arm, forearm, calf, mid-thigh, hips/thighs, and buttocks/hips circumferences were associated with decreases in age-adjusted NIHTB-CB composite scores. Interestingly, changes in waist circumference were not associated with changes in age-adjusted NIHTB-CB composite score (p=0.77). We also found that amongst participants with in-person follow-up (n=66), decreases in triglycerides associated with decreases in Rey AVLT delayed recall (PE: 0.005, 95%CI: 0.001, 0.01) and, amongst all participants (in-person or virtual follow-up, n=87), decreases in weight was associated with decreased Rey AVLT delayed recall (PE: 0.01, 95%CI: 0.001, 0.02).

Association between change in diabetes complications and change in cognition (Table 3)

No changes in diabetes complications were significantly associated with changes in NIHTB-CB composite or Rey AVLT delayed recall scores following bariatric surgery.

Association between baseline diabetes complications and change in cognition (Table 3)

Higher baseline eGFR was associated with decreased NIHTB-CB (PE: -0.23, 95%CI: -0.42, -0.04). In contrast, better baseline retinopathy measurements (higher mean deviation on FDT testing) were associated with increased NIHTB-CB at follow-up (PE: 1.18, 95%CI: 0.30, 2.07). Other baseline diabetes complications were not associated with changes in Rey AVLT delayed recall score following bariatric surgery.

Discussion

Two years following bariatric surgery and substantial improvements to metabolic risk factors, we found age-adjusted cognition was generally stable in patients with class II/III obesity. Since individuals with obesity experience more rapid cognitive decline versus individuals without obesity (23), stable cognition at 2-year follow-up after bariatric surgery may be considered a success against historical trends; however, future controlled trials are needed to further test this hypothesis. We found one secondary outcome related to executive function, dimensional card sorting test, significantly improved, while another secondary outcome related to memory, Rey AVLT delayed recall, worsened following surgery. Surprisingly, we found that reduced waist circumference was not associated with cognitive change after surgery despite the correlation between larger central obesity to poorer cognitive function (4).

The stable composite cognition and ameliorated secondary outcome we observed are improvements compared to historical trends, but not fully aligned with previous studies (10). A recent meta-analysis of 20 studies representing 8 unique populations suggested that bariatric surgery generally, but not universally, improved aspects of memory, but not executive function or attention. However, previous studies were smaller, with relatively shorter-term follow-up, and assessed cognition using a variety of tests, which often did not examine a composite score of multiple cognitive domains (10). Of the 20 studies included in the meta-analysis (10, 13) studies reported cognitive assessments from a single population, the Longitudinal Assessment of Bariatric Surgery Cohort (LABS). The LABS study assessed changes in cognition at 12 weeks (n=109) (24), 12 months (n=95) (25), 24 months (n=63) (26), 36 months (n=50) (27), and 48 months (n=21) (27) after bariatric surgery compared to control groups at 12 and 24 months. LABS found

Table 3. Association between changes in cognition and changes to metabolic factors and diabetes complications following bariatric surgery

	NIHTB-CB composite score (n=66)	Rey AVLT Delayed Recall (Completed follow-up in-person, n=66)	Rey AVLT Delayed Recall (Completed follow-up in-person or virtual, n=87)
Weight	0.15 (-0.06, 0.35)	0.006 (-0.007, 0.02)	0.01* (0.001, 0.02)
SBP	0.17 (-0.02, 0.36)	-0.005 (-0.02, 0.01)	Not Collected Virtually
Fasting Glucose	0.08 (-0.15, 0.30)	0.01 (-0.01, 0.02)	Not Collected Virtually
HDL	-0.05 (-0.35, 0.25)	-0.01 (-0.03, 0.01)	Not Collected Virtually
Triglycerides	0.003 (-0.05, 0.06)	0.005* (0.001, 0.01)	Not Collected Virtually
HbA1c	3.45 (-2.26, 9.19)	-0.09 (-0.46, 0.28)	Not Collected Virtually
Low Waist Circumference	0.04 (-0.20, 0.27)	0.005 (-0.01, 0.02)	0.009 (-0.004, 0.02)
Arm Circumference	0.89* (0.13, 1.65)	-0.01 (-0.07, 0.05)	0.007 (-0.04, 0.05)
Forearm Circumference	1.43* (1.00, 3.26)	0.05 (-0.05, 0.15)	0.04 (-0.04, 0.12)
Calf Circumference	2.15* (1.05, 3.26)	0.03 (-0.05, 0.12)	0.03 (-0.03, 0.10)
Mid-Thigh Circumference	0.79* (0.32, 1.26)	0.02 (-0.01, 0.06)	0.02 (-0.002, 0.05)
Hips/Thighs Circumference	0.63* (0.27, 1.00)	0.02 (-0.01, 0.04)	0.02 (-0.002, 0.04)
Abdomen Circumference	0.13 (-0.08, 0.34)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)
Buttocks/Hips Circumference	0.35* (0.02, 0.68)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.02)
High-Waist Circumference	0.08 (-0.16, 0.31)	0.002 (-0.01, 0.02)	0.007 (-0.005, 0.02)
Peripheral Neuropathy: IENFD Leg	0.73 (-0.3, 1.49)	0.002 (-0.05, 0.06)	Not Collected Virtually
Peripheral Neuropathy: IENFD Thigh	0.38 (-0.06, 0.35)	0.004 (-0.007, 0.02)	Not Collected Virtually
CAN: E/I Ratio	-30.37 (-63.58, 2.854)	-0.94 (-3.04, 1.16)	Not Collected Virtually
CKD: eGFR	0.24 (-0.04, 0.51)	-0.01 (-0.03, 0.01)	Not Collected Virtually
Retinopathy: Mean Deviation FDT	-0.87 (-2.20, 0.46)	-0.01 (-0.08, 0.07)	Not Collected Virtually
Peripheral Neuropathy: IENFD Leg (baseline)	-0.40 (-0.89, 0.09)	0.01 (-0.03, 0.05)	Not Collected Virtually
Peripheral Neuropathy: IENFD Thigh (baseline)	-0.18 (-0.59, 0.24)	-0.02 (-0.05, 0.1)	Not Collected Virtually
CAN: E/I Ratio (baseline)	12.75 (-15.29, 40.79)	-0.20 (-2.19, 1.79)	Not Collected Virtually
CKD: eGFR (baseline)	-0.23* (-0.42, -0.04)	0.01 (-0.003, 0.03)	Not Collected Virtually
Retinopathy: Mean Deviation FDT (baseline)	1.18* (0.30, 2.07)	0.03 (-0.03, 0.09)	Not Collected Virtually

* Indicates statistical significance ($p<0.05$) based on a two-sided p-value. Each row represents a single model adjusted for age, sex, baseline BMI, and baseline outcome. Certain metabolic risk factors and diabetes complications measurements were not collected during virtual follow-up assessments, therefore these results are not reported. NIHTB-CB composite score models were adjusted for sex, baseline BMI, baseline WRAT-4, and baseline NIHTB-CB composite score (the outcome is already adjusted for age). Rey AVLT delayed recall models were adjusted for age, sex, baseline BMI, baseline WRAT-4, and baseline Rey AVLT delayed recall., SBP, systolic blood pressure; HDL, high-density lipoprotein; HbA1C, hemoglobin A1c; IENFD, intraepidermal nerve fiber density; CAN, cardiovascular autonomic neuropathy; E/I ratio, expiration/inspiration ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FTD, frequency doubling technology.

that memory improved 12 weeks following bariatric surgery (24), which was sustained through 36 months (27). In addition, consistent with our finding, the LABS study found executive function steadily increased and was statistically significant at 36 months (27). In contrast, attention increased until 24 months, but declined to near baseline levels at 36 months (27). Outside of the LABS cohort, findings were inconsistent, and based on smaller cohorts with shorter follow-up periods. In particular, six other cohort studies found improved cognitive assessments at 4 months (n=10 (28) and n=11 (29)), 6 months (n=8 (30) and n=36 (31)), and 12 months (n=22 (32) and n=8 (33)), following surgery. In contrast, two cross-sectional studies (n=30 (34) and n=50 (35)) and three cohort studies with follow-up periods of 4 months (n=12 (36)) and 6 months (n=40 (37) and n=17 (38)), found no differences in cognitive function following surgery.

To date, our current study is the largest (n=87) to assess changes in cognition at 2-year follow-up after bariatric surgery, followed closely by the LABS study (n=63) (10). However, the impact of bariatric surgery on cognition remains unclear due to the conflicting evidence between our study, which found stable cognition, the meta-analysis (10) which found improved memory, and the LABS studies, which found improved memory and executive functioning. While both the LABS studies and our study found improved executive functioning, only the LABS studies found improved memory. One potential explanation for the conflicting results is that our study was primarily made up of individuals that completed a sleeve gastrectomy, whereas the LABS studies were conducted on individuals that underwent gastric bypass surgery. Therefore, potential differences stemming from these different bariatric surgeries may have contributed to differential cognitive changes across studies, such as magnitude of improved metabolic risk factors (39), prevalence of nutritional deficiencies (40), gastroesophageal reflux disease (39), and dumping syndrome (41). Indeed, the recent meta-analysis found that sleeve gastrectomies had smaller changes to cognitive domains compared to gastric bypass surgeries (10). Another possible explanation is that the benefits of sleeve gastrectomy to memory may take longer to manifest. The two study populations differed demographically; our present study included a slightly older population (mean ages 46.8 versus 42.3) consisting of fewer females (73.6% versus 90.5%) compared to the LABS cohort (26). In addition, baseline NIHTB-CB composite score was above average in the present study, potentially limiting our ability to discern an impact from bariatric surgery on cognition. Lastly, residual unmeasured confounding, such as exercise or other underlying comorbidities, may have led to differences in our populations. Thus, overall, to provide the best evidence on the effectiveness of bariatric surgery on cognition and potential differences amongst bariatric surgery types, large observational studies with precise measures of confounding variables and/or randomized controlled trials are needed. Additionally, longer-term studies are needed to determine if cognitive changes following bariatric surgery ultimately reduce the risk of dementia. On the other hand, consistent with the LABS study, we found that one secondary outcome, the dimensional card sorting test of executive function, significantly improved. Considering this was a secondary study outcome, this finding should be interpreted with caution. However, given executive functioning is the most critical cognitive domain for retaining activities of daily living (42), improvement in this domain could have important functional implications.

Although metabolic risk factors have previously been found to correlate with cognitive decline (3, 6, 7), in the present study, no improvements in any individual metabolic risk factor associated with improvements to cognitive function. In this same population, prior to bariatric surgery, we previously reported that waist circumference was the most important risk factor for reduced cognition, even after adjusting for a comprehensive set of risk factors (4, 5). Therefore, we were surprised to find that reduced low-waist circumference, measured at the top of the iliac crest, was not associated with improved cognition. However, our results are in agreement with two previous studies that did not find associations between BMI changes to cognitive changes following bariatric surgery (25, 26, 43). Our study may have lacked statistical power to detect such associations, although it is also possible that the effect of waist circumference reduction is secondary in importance compared to other factors after surgery. On the other hand, we found that greater reductions in circumferences at the arm, forearm, calf, mid-thigh, hips/thighs, and buttocks/hips were associated with greater cognitive decline following bariatric surgery. Future studies with larger sample sizes are needed to further investigate our unexpected findings.

In addition to improved metabolic risk factors, patients who undergo bariatric surgery reap numerous additional wide-ranging pleiotropic benefits. For example, patients completing bariatric surgery report improved mental health profiles, including fewer depressive symptoms, better mood, social functioning, and health-related quality of life (44), increased physical activity and better eating behaviors (45), increased social activity, reduced polypharmacy46, and reduced risk of obstructive sleep apnea (47). Given that each of these comorbidities have been established as risk factors for cognitive function and/or decline (48–52), improvement amongst these factors may explain why bariatric surgery has a beneficial impact on brain health for individuals with obesity. Previous analyses from the LABS cohort assessed association between certain baseline risk factors to cognitive changes following bariatric surgery, finding that baseline alkaline phosphatase (53), family history of Alzheimer's disease (54), and serum leptin and ghrelin (55) correlated with cognition 12 months after bariatric surgery. In contrast, analyses of the LABS cohort found that age (56), history of binge eating disorder (57), history of depression (58), baseline cystatin C (53), and change in C-reactive protein (59) did not influence cognitive function 12 months following bariatric surgery. Future, larger controlled studies are needed to identify what specific changes in these wide-ranging risk factors after bariatric surgery contribute the most to improved cognitive function for individuals with obesity. However, it is likely that bariatric surgery's unique capability of simultaneously ameliorating multiple risk factors is one reason that cognitive outcomes are possibly improved compared to the natural history of those with obesity.

We found that improvements in diabetes complications were not associated with improvements in cognition following bariatric surgery. Although several studies found diabetes complications are linked to cognition (9, 60, 61), to our knowledge, this is the first study that assessed this relationship following bariatric surgery. Specifically, we found a trending, but not statistically significant, correlation between improved sensitive peripheral neuropathy measures (IENFD of the distal leg [p-value=0.06] and proximal thigh [p-value=0.08]) and CKD (measured by eGFR [p-value=0.09]) and improved NIHTB-CB composite score. Our study may have lacked statistical power to detect these associations. Therefore, it remains unknown whether changes in diabetes complications modify the effect of bariatric surgery on cognition or vice versa. It also remains unclear whether the beneficial effects of surgery simultaneously influence each complication through a distinct pathophysiology or through similar mechanisms. Regardless of the underlying mechanism, our results provide some preliminary evidence that bariatric surgery may effectively and simultaneously improve metabolic profiles, diabetes complications, and cognitive function for individuals with obesity, although future studies are needed.

Our study limitations include a relatively small sample size. However, to date, our study was the largest to assess changes in cognition at 2-year follow-up post bariatric surgery. Our study also only included 10 (11.5%) participants that completed gastric bypass surgery, thereby limiting our ability to compare cognitive changes between gastric bypass and sleeve gastrectomy surgeries. In addition, some participants (23.0%) were lost to follow-up, and our study included no intermediate assessments of cognition. Therefore, we were unable to include participants lost to follow-up in our analysis of cognitive change. Lastly, although our cognitive assessments adjusted for participant age at baseline and follow-up, our study lacked a control group without bariatric surgery. Therefore, future studies are needed to determine if the observed cognitive changes were different from that of normal aging within participants with obesity.

Furthermore, although we adjusted for sex in our analysis, our study included majority (73.6%) females, limiting generalizability of our findings to males. In addition, some participants (23.0%) were lost to follow-up. Lastly, we only assessed mood at baseline, therefore, we were unable to determine how changes to mood may have impacted changes in cognition after bariatric surgery.

Following bariatric surgery, we found age-adjusted cognition in a cohort of individuals with class II/III obesity was stable. Stable age-adjusted cognition is likely an improvement against the natural history of cognitive decline in individuals with obesity. One secondary measurement of executive function improved, suggesting surgery may have some important cognitive benefits in this population, although one measure of memory declined. Improvements to diabetes complications and metabolic risk factors surprisingly did not associate with improved cognition. Future larger and longer-term studies are needed to determine definitively whether bariatric surgery prevents cognitive impairment and ultimately dementia, and if so, the underlying mechanisms leading to these improvements.

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