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Diabetes & Obesity International Journal
ISSN: 2574-7770

Diabetes, Obesity-Associated Comorbidities and NIH-Toolbox Neurocognitive Performance

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Investigation Paper
Volume 6 Issue 1
Received Date: January 01, 2021
Published Date: January 25, 2021
DOI: 10.23880/doij-16000236

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Abstract

Background/Objectives: Severe obesity is associated with cognitive deficits in adults without current or past neurological brain disturbances. This study examined the relationship between specific metabolic and vascular risk factors and cognitive performance on a computerized neurocognitive assessment battery in adults with BMI > 35.

Subjects/Methods: 123 adults with Class II or III obesity, ages 20-75, were enrolled in a study of the cognitive and brain effects of reduced BMI and improved diabetes mellitus (DM) following bariatric surgery. Baseline clinical/cognitive assessments were conducted with the NIH Toolbox (NIH-TB) cognitive module prior to surgery, and in severely obese controls recruited from the community. Global, Fluid and Crystallized indices were derived from performance across nine tasks. Hierarchical regression analyses examined six obesity-associated clinical factors (BMI, HbA1c, and DM, hypertension, sleep apnea, and osteoarthritis diagnoses) relative to NIH-TB performance.

Results: Fluid Cognition deficits were observed, greatest on attention-executive and cognitive processing speed tasks (Flanker and Pattern Comparison). DM diagnosis was most strongly associated with weaker cognitive performance (Global and Fluid Cognition), and with poorer performance on the Flanker, Pattern Comparison, Picture Sequencing, Verbal Learning, and Symbol Coding tasks. Elevated HbA1c was associated with weaker Card Sorting and Symbol Coding performance, hypertension with poorer Fluid Cognition, and osteoarthritis with lower List Sorting performance. Elevated BMI was only associated with Flanker performance, though DM was more strongly associated with this measure.

Conclusion: Deficits of fluid cognitive functions (attention-executive, processing speed) exist among adults with Class II and III obesity. DM was most consistently associated with weaker NIH-TB performance. BMI was not as strongly associated with NIH-TB performance, perhaps reflecting the elevated BMI of the entire sample. That cognitive deficits were linked to specific obesity-associated comorbidities support the validity and potential clinical utility of the NIH-TB for the assessment and management of adults with severe obesity.

Keywords: NIH Toolbox; Obesity; Diabetes Mellitus; Cognitive Deficits

Abbreviations: BMI: Body Mass Index; DM: Diabetes Mellitus; OSA: Obstructive Sleep Apnea; CPAP: Continuous Airway Pressure; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; MoCA: Montreal Cognitive Assessment.

Background

Severe obesity is occurring globally with increasingly high prevalence [1,2], contributes to reduced functional and health status [3-5], and is associated many common medical comorbidities, including type-2 diabetes [6,7], hypertension and cardiovascular disease [8], and sleep disorders [9]. Though less widely recognized by the general public, obesity is also associated with reduced cognitive performance and an increased prevalence of neurocognitive deficits [10,11]. We previously found that elevated body mass index (BMI) is not only associated with cognitive deficits among adults with severe obesity [12-14], but that cognitive improvements occur after significant weight loss following bariatric surgery [15,16]. Yet, the factors underlying obesity-associated cognitive deficits is not well understood. Cognitive dysfunction could occur as a function of having an elevated BMI in its own right, or may be a byproduct of comorbidities that are common among adults with severe obesity.

Evidence that elevated BMI is associated with reduced cognitive performance comes from epidemiological studies often examining either the adults in the general population or otherwise healthy community samples [12,13,17]. These studies have linked obesity not only to reduced cognitive performance, but also risk for developing dementia. Yet, in many of these studies elevated BMI is not alone in its association with cognitive functioning, as other risk factors and medical etiologies common in adults with severe obesity also have been shown to contribute to cognitive dysfunction, type-2 diabetes mellitus (DM) [18], hypertension [19], other vascular etiologies and risk factors [20,21], and obstructive sleep apnea (OSA) [22]. The cumulative effects of hypertension and diabetes on cognition was found to be greater than the effects of either etiology alone in the Framingham study [23], and there is also some evidence of interactions between these etiologies and other vascular and metabolic factors on cognition [24].

The majority of past research on this topic has focused on the interactive effects on cognition of obesity with a single etiology or risk factors. For example, DM has been shown to exacerbate the adverse effects of elevated BMI on cognition and the brain [25-27], though this has not been observed in all studies [28]. In another study, elevated BMI was actually found to be weakly associated with better cognitive performance in the elderly [25]. Vascular comorbidities of obesity can also affect cognition. For example, we previously found that obesity and also hypertension contributed to weak cognitive performance among patients with heart failure [29], though this has not been a ubiquitous finding across all studies [20,26,30,31]. Studies examining OSA in the context of obesity also provided mixed results with respect to their combined effect on cognition. It is well established chronic OSA contributes of cognitive and brain disturbances [22], and treatment with continuous airway pressure (CPAP) improves cognitive functioning in adults with OSA [32]. Yet, disentangling the effects iof OSA in the context of comorbid obesity has been challenging [33,34]. In a study from the LABS cohort, cognitive improvements following bariatric surgery were not attributable to reduced OSA [35]. Obesity exacerbates other medical conditions as well. For example, elevated BMI in the context of HIV is associated with weaker congitive performance [36].

Several factors contribute to ambiguities in past research regarding the contribution of comorbidities such as DM to obesity-associated cognitive deficits [12,27,37,38]. Often comorbidities are treated as covariates to control for experimental confound rather than being analyzed as a predictive factor per se. Studies focusing on the effects of obesity in health adults often excluded potential participants with certain comorbidities to eliminate their confounding influence. Furthermore, a majority of past findings on obesity, comorbidities, and cognition have come from either epidemiological study of large populations or community samples consisting of adults who are representative of general public. Consequently, there is typically a wide BMI range, and comorbidities are present at a rate consistent with their overall prevalence. While this can be informative to address questions about normative characteristics, it is not optimal for determining the relative impact of BMI or particular comorbidities among adults who are severely obese, many with multiple medical risk factors and etiologies certain types of information typically is present in a very wide range of BMI occurs other variables cohorts.

Relatively few studies to date have focused specifically on cognitive performance as a function of the multiple vascular and metabolic comorbidities that often occur in conjunction with severe obesity. When this question was addressed, it was in the context of a broader study not necessarily designed with cognitive or brain dysfunction as a primary focus. For example, the LABS study was designed to evaluate bariatric surgery outcome, and factors that influenced this outcome. Cognition was examined in a supplementary study that was constrained to some extent by the requirements and logistics of the parent study.

The NIDDK-funded R01 parent study (DK09933401) that served as the basis for the current study was explicitly designed and is being conducted to achieve greater

understanding of the factors that contribute to cognitive and brain dysfunction in adults with Class II and Class III obesity, most with one or more comorbidities, including DM. While the larger aim of the project is to determine the basis for improvements in cognitive and brain functioning following significant weight lost secondary to bariatric surgery, the current analyses focus on clinical factors, including BMI and comorbid conditions that affect cognitive performance at baseline. Several possibilities exist: 1) Cognitive deficits in this cohort may be primarily a manifestation of elevated BMI itself; 2) A specific comorbid condition, such as DM may be the primary determinant of cognitive dysfunction; or 3) Obesity-associated comorbidities may interact either cause or exacerbate cognitive deficits occurring in the context of severe obesity. The cognitive module of the NIH-ToolBox (NIH-TB) was administered to assess performance across multiple cognitive domains. The presence and severity of several common comorbidities of obesity (DM, hypertension, OSA, osteoarthritis) was determined from combined information from medical records and participant-reported medical history. Laboratory measures were also collected (hbA1C, fasting glucose, polysomnogram results). These clinical and laboratory measures along with BMI, and demographic variables were entered into hierarchical regression models to determine their relationship to cognitive performance on the NIH-TB. We hypothesized that greater BMI would be associated with weaker cognitive performance, that DM would also contribute to cognitive deficits, and that other comorbidities (e.g., OSA) might adverse impact cognition as well. We hypothesized that DM would be the comorbidity most strongly associated with reduced cognitive performance based on the clinical research literature on DM and brain functioning.

Methods

Study Design

This study analyzed data acquired form from Weight Loss Intervention and Surgical Effects (WISE Brain) study at the University of Florida. This study was part of a larger longitudinal project funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to better understand the mechanisms underlying the effect of severe chronic obesity on cognition and the brain. The study is designed to determine if improved cognitive performance following bariatric surgery is associated with enhanced brain functioning secondary to cerebral metabolic and hemodynamic changes occurring after significant weight loss. The current paper is based on results of analyses conducted on data acquired from baseline assessment of WISE Brain study cohort of pre-surgical and non-surgical participants.

Participants

Study inclusion criteria included: age between 21 and 75 years and BMI > 35.0. Exclusion criteria included: score on the Montreal Cognitive Assessment (MoCA) score < 20; history of neurological disorder or injury or severe psychiatric illness (e.g., schizophrenia); severe cardiovascular disease; unstable medical condition (e.g., cancer). A total of 123 patients were included in the current study between the ages of 23 and 73 (age: 46.98 ± 12.75) years. The study sample had an average BMI of 45.15 (BMI : 45.15 ± 8.04) with 65.9% meeting criteria for Class III obesity (BMI ≥ 40.0), and 33.3% for Class II (BMI of 35.0 – 39.9). The sample included participants who were seeking to undergo bariatric surgery (n = 81), and non-surgical community members (n = 42). Non-surgical participants were recruited to serve as controls for future post-operative comparison with the bariatric surgery group. There were significantly more females (74.0%) than males in the sample, reflecting gender differences in adults undergoing bariatric surgery as well as community interest in weight related research. The majority of participants we Caucasian (68.3%). On average, participants had approximately two years of college (education: 13.95 ± 2.72 years). Demographic and clinical characteristics of the study sample are presented in Table 1.

Characteristic	Total sample (N = 123)	Bariatric patients (N = 81)	Obese controls (N = 42)
Age (yr.)	46.98 ± 12.75	44.14 ± 12.20	52.45 ± 12.11
Gender (% women)	74	76.5	69
Education (yr.)	13.95 ± 2.72	14.06 ± 2.79	13.74 ± 2.60
Race (% Caucasian)	68.3	70.4	64.3
Hypertension (% [n])	57.7 [71]	64.2 [52]	45.2
Number of comorbidities (%)	--	--	--
None	16.3	12.3	23.8
One	24.4	22.2	28.6

Two	29.3	33.3	21.4
Three	22.8	24.7	19
Four	7.3	7.4	7.1
BMI (kg/m2)	45.15 ± 8.04	47.10 ± 8.42	41.39 ± 5.67
Class Obesity (%)	--	--	--
Class II	33.3	22.2	54.8
Class III	65.9	77.8	42.8
Type-2 diabetes (% [n])	35.8 [44]	35.8 [29]	35.7 [15]
HbA1c	6.34 ± 1.32	6.40 ± 1.49	6.25 ± 0.98
Normal (% [n])	58.5 [72]	56.8 [46]	61.9 [26]
Elevated (% [n])	22.8 [28]	19.8 [16]	28.6 [12]
CPAP use (% [n])	25.2 [31]	28.4 [23]	19.0 [8]
Sleep apnea (% [n])	48.0 [59]	54.3 [44]	35.7 [15]
Arthritis (% [n])	39.0 [48]	38.3 [31]	40.5 [17]
Depression (% [n])	36.6 [45]	42.0 [34]	26.2 [11]

Table 1: Demographic and medical characteristics of total sample, bariatric surgery participants, and obese controls (continuous variables reported as mean ± SD, and categorical variables as percentages).
Note: * BMI = body mass index; CPAP = continuous positive airway pressure.

Procedures

The local Institutional Review Board (IRB) approved the study procedures, and all participants provided written informed consent prior to study enrollment. Prospective research participants were recruited after indicating interest during an initial evaluation for bariatric surgery, or if they responded to advertising fliers. All participants completed a medical history evaluation, a neuropsychological assessment battery, and several self-report questionnaires. In addition, participants underwent MR assessment and polysomnography test (if never assessed for OSA or not using CPAP therapy). A small blood sample was collected for HbA1c determination and for future analyses of other laboratory biomarkers.

Measures

Demographic and Medical History: History of hypertension, diabetes, apnea, BMI, and CPAP therapy in addition to history of depression and pertinent demographic data, was collected through self-report or through review of available medical records. Hemoglobin A1c (HbA1c) levels were also measured, which indicates average plasma glucose concentration. Reported as a percentage value, it is used to diagnose pre-diabetes or type-2 diabetes and serves as a useful indicator of disease severity. Results between 5.7% and 6.4% indicate pre-diabetes while 6.5% or higher is classified as diabetic.

NIH-ToolBox Cognitive Assessment: All participants were administered the cognitive module of the NIH Toolbox for the Assessment of Neurological and Behavioural Function (NIH-TB). This computerized IPAD-based cognitive assessment battery consists of nine tasks from which three composite scores are derived including measures of Overall Cognition, and sub-components of Crystalized and Fluid Cognition. Crystallized cognition is a measure of verbal ability, which typically improves until middle-age and subsequently remains stable throughout adulthood (Akshoomoff-31). *Fluid cognition* measures problem-solving, decision-making, and memory encoding ability and begins to decline after middle-age (Akshoomoff-31), and is less stable than crystalized cognition as it varies as a function of various internal and external factors that can affect performance at a given point in time. The Crystalized Cognition composite score is derived from the standard scores on Oral Reading Recognition and Picture Vocabulary tests. The Fluid Cognition is derived from the standard scores on five tests (Card Sorting, Flanker, List Sorting, Pattern Recognition, Picture Sequencing).The overall cognition composite score is based on an average of fluid and crystallized cognition scores. Two additional supplementary tests that optimal measures of the NIH-TB were also administered (Auditory Verbal Learning Test, Oral Symbol Digit Test). A description of each test is provided below. More detailed information on the NIH-TB and each cognitive test is available in the "NIH Toolbox Scoring and Interpretation Guide for the iPad" developed by the National Institutes of Health in collaboration with investigators at Northwestern University (NIH-30).

- **Picture Vocabulary Test:** Participants are asked to choose a picture on the screen that best corresponds

to a word that is spoken. It is a measure of vocabulary knowledge and a strong measure of crystallized intelligence.

- **Oral Reading Recognition Test (Reading):** Participants are asked to read words presented on the screen to the best of their ability. This is another measure of vocabulary and crystallized intelligence.
- **Flanker Inhibitory Control and Attention Test (Flanker):** A row of arrows is presented to the participant, alternating between all arrows pointing in the same direction or some pointing in different directions (congruence vs. incongruence). The participant must then choose the direction that the middle arrow is pointing as quickly as possible. A combination of accuracy and reaction time yields an overall score which measures executive function, particularly attention and inhibitory control.
- **Dimensional Change Card Sort Test (DCCS):** Participants are asked to choose a picture on the screen which is either the same color or same shape as the target picture. This is another measure of executive function, specifically cognitive flexibility, with scoring based on a combination of accuracy and reaction time.
- **Picture Sequence Memory Test (PSMT):** Participants are asked to recall the order of a series of pictures that were previously presented while corresponding audio describing each picture is played. This is a measure of episodic memory, a subset of fluid ability.
- **List Sorting Working Memory Test (List Sorting):** Pictures of food and animals are presented one at a time on the screen. In the initial trial, participants are asked to recall pictures of food or animals in size order from smallest to biggest. Subsequently, participants are asked to recall the pictures in order of food first, in size order from smallest to biggest and then animals in order of increasing size. This is a measure of working memory, a subset of fluid ability.
- **Pattern Comparison Processing Speed Test (Pattern Comparison):** Participants are asked to choose whether two pictures are the same or not the same as quickly as possible. This measures speed of processing, which is another fluid ability measure.
- **Auditory Verbal Learning Test (Rey):** Participants are asked to recall as many words as possible after a series of words are presented via audio for three trials. Higher raw scores indicate better episodic memory.
- **Oral Symbol Digit Test:** Participants are asked to verbalize as quickly as possible which numbers correspond to each symbol presented on a page, with a coding key available at the top of the page. Higher raw scores indicate better processing speed.

Data Analysis

Descriptive statistics were used to characterize the overall sample and the relationships between medical comorbidities. Chi-square analyses were used to compare concurrence of diagnosis with various biomarkers or treatment, such as incidence of diabetes diagnosis and measured HbA1c blood levels, as well as history of apnea among individuals using CPAP therapy versus non-treatment. Similar analyses were conducted to assess CPAP use, HbA1c levels, and prevalence of medical comorbidities across obesity class. T-tests and chi-square analyses were used to examine differences between the bariatric surgery and control groups for all demographic and clinical measures. For purposes of subsequent analyses two groups were pooled, since bariatric surgery effects were not being examined.

Imputation procedures were employed to compensate for missing cognitive and medical data. There were several reasons for missing data: 1) Non-completion of a NIH-TB task; 2) Technical problems resulting in errors in the IPAD administration or storage of data from a task; and 3) Unavailability of a particular clinical variable from available medical records related. Visual inspection did not reveal any systematic pattern to missing data, and analysis of the frequency of missing values did not vary as a function of any demographic or clinical grouping Thus, data were treated as *Missing Completely At Random*. To minimize sample loss, using IBM SPSS Version 26, we conducted 25 multiple imputations. We used the fully conditional specification method. The imputation model included all the variables used in the regression analyses (both independent and dependent variables), although we only estimated independent variables/predictors. We then conducted a stepwise regression including all possible predictors for each cognitive predictor, and recorded which predictors were selected in more than 50% (i.e., 13) of the imputed data sets. In a second step, we conducted a final simultaneous regression with the identified predictors for each dependent variables. Estimates shown in the results below are pooled estimates that account for the variability in estimates between and within the imputed data sets. In addition to the pooled estimates, result below show the range of r-squared estimates for the full set of 25 imputations for each cognitive outcome.Two sets of hierarchical regression analyses (backward elimination) were conducted to determine the clinical etiological/risk factors associated with cognitive performance. In the first set of regression analyses, the Overall Cognition, Crystalized, and Fluid Cognition scores served as dependent measures in three separate models. In the second set of hierarchical regressions analyses, the individual NIH-TB test scores served as dependent measures in separate models. For all these regression analyses, six etiological/risk factors were entered as independent

measures (BMI, Diabetes, HbA1C, HTN, OSA, Arthritis) first hierarchical stage, along with four demographic/clinical covariates (sex, race, years of education, BDI score) in the second hierarchical stage. For two regression models (AVLT, Oral Symbol Digit), age was also entered as a covariate at the second stage, as age-adjusted norms were not available for these NIH-TB tests.

Results

Clinical Characteristics

In addition to meeting the clinical criteria for obesity, the majority of participants experienced at least one comorbidity (83.7%). Many had multiple comorbidities: 7.3% of the sample had four or more comorbidities, 22.8% had three, and 29.3% had two. Hypertension was the most prevalent comorbidity with 57.7% of the sample having a clinical diagnosis. Obstructive Sleep Apnea (OSA) was diagnosed in 48.0% of the sample. However, only 25.2% reported using a CPAP machine. A. Hypertension also demonstrated a significant relationship to HbA1c levels ($r = .316$, $p < 0.01$, $N = 100$) and type-2 Diabetes Mellitus (DM) diagnosis ($r = .221$, $p < 0.05$, $N = 122$).OSA diagnosis and HbA1c level was positively correlated ($r = .218$, $p < 0.05$, $N = 115$), as was the correlation between diabetes diagnosis and CPAP use ($r = .190$, $p < 0.05$, $N + 115$).

Approximately 35.8 % of participants were diagnosed with DM, with 22.8% experiencing elevated HbA1c levels (6.34 ± 1.32) at the time of assessment. Patients are considered diabetic if they experience HbA1c levels of 6.5 or higher. While HbA1c levels and DM are highly correlated ($r = -.566$, $p< 0.01$, $N=99$), cross-tabulation calculations revealed that a fourth of participants with elevated HbA1c levels did not have a formal DM diagnosis. Conversely, 25% of participants with a DM diagnosis did not have elevated HbA1c levels. In addition to being related to hypertension and OSA, as previously discussed, HbA1c levels demonstrated a correlation to an arrhythmia diagnosis ($r = .262$, $p < 0.05$, $N = 100$) and DM was inverse related to BMI ($r = -.187$, $p < 0.05$, $N = 122$).

Bariatric surgery candidates reported higher rates of all comorbidities with the exception of Arthritis. Arthritis was reported in 38.3% of surgical participants and 40.5% in community participants. However, this difference was not statistically significant ($r= .021$, $N = 123$). A significant inverse relationship was observed between obesity class and arthritis diagnosis. Participants with Class III obesity were more likely to have arthritis when compared to Class II participants ($r = -.197$, $p < 0.01$, $N=123$). No other comorbidities or demographic characteristics were found to significantly relate to arthritis.

Neurocognitive Performance

Table 2 provides performance data on the NIH-TB neurocognitive measures for the entire sample, including Total Cognition, Fluid Cognition, and Crystalized Cognition composite scores, and mean Standard Scores for seven NIH-TB tasks sensitive to the domains of attention, executive functioning (set shifting), reaction time, cognitive processing speed, working memory, and verbal learning and recall.

Composite Measures	Standard Score	% > - SD
Overall Cognition	100.3 (1.5)	17.6
Fluid Cognition	96.2 (1.7)	26.2*
Crystalized Cognition	104.6 (1.4)	12.8
Domain Specific Measures	**Standard Score**	**% < 1 SD**
Card Sort	96.6 (1.7)	21.5
Flanker Task	90.9 (1.4)	40.0*
List Sequencing	102.4 (1.4)	17.1
Pattern Comparison	94.8 (1.9)	33.6*
Picture Sequencing	100.9 (1.4)	12.3
Oral Recognition	106.9 (1.7)	6.5
Picture Vocabulary	103.3 (1.2)	8.9

Table 2: NIH-TB Cognitive Performance.

Note: *p<.05, Age-adusted Standard Scores (SS: mean + standard error) are provided for each cognitive measure. A SS = 100 indicates performance at the 50th %tile relative to normative NIHTB data with one standard deviation (SD) = 15. Participants with scores greater than one SD below the mean (i.e., < 13th %tile) have at least mild deficits relative to NIHTB normative data and also compared to their own performance on the verbal measures used to calculate Crystalized Cognition.

Participants in the sample did not exhibit severe neurocognitive dysfunction (i.e., scores greater than two standard deviations below the mean for the NIH-TB normative sample), as both their Overall Cognition was average (100.3+1.5) was average, and their Crystalized Cognition (104.6+1.4) was very consistent with estimated pre-morbid intelligence on the BARONA (*M* = 103.8, *SD* = 8.7). Fluid Cognition (96.2+1.7), while in the average range was significantly below Crystalized Cognition and also below their BARONA estimated premorbid intelligence (p<.05). A significant proportion of participants (26.2%) had Fluid Cognition scores that were greater than one standard deviation below average (p<.05), indicating mild Fluid Cognition deficits. On domain specific measures, a significant percentage of participants (p<.05) also had domain specific deficits on the Flanker (40.0%) and Pattern Comparison (33.6%) tasks, measures of attention and cognitive processing speed.

Clinical Factors Associated with NIH-TB Performance

The relationships differed for the three cognitive composite indices. Obesity-associated comorbidities were significantly associated with Total Cognition and Fluid Cognition, but not Crystalized Cognition (see Table 3). DM diagnosis had a significant negative relationship with Overall Cognition (β = -.39, p < .01) with weaker performance among participants with DM. Two comorbidities (DM: (β = -.26, p < .01); HTN: (β = -.23, p < .05) were significantly associated with Fluid Cognition, with weaker performance among participants having these comorbidities. In contrast, Crystalized Cognition was significantly associated with only demographic variables (education, sex, race).

NIH-TB Measure	Model	β	R
Overall Cognition	Diabetes	-.39 **	.59***
	Education	.35 **	
	Sex	-.28 **	
	Race	-.22 *	
Fluid Cognition	Diabetes	-.26**	.41**
	HTN	-.23 *	
	Sex	-.20 *	
Crystalized Cognition	Education	.54***	.68***
	Sex	-.21 *	
	Race	-.26 *	
Card Sorting (Executive)	HbA1c	-.30 *	.30 *
Flanker Task (Processing Speed)	Diabetes	-.37***	.54***
	BMI	-.25 *	
	Sex	-.27 **	
	Race	-.23 **	
List Sorting (Working Memory)	Arthritis	-.20 *	.39**
	Sex	-.38**	
Picture Sequencing	Diabetes	-.25#	.25#
Pattern Comparison	Diabetes	-.34*	0.35
Symbol Coding	Diabetes	-.50**	.63***
	HbA1C	-43*	
	Age	-43	
Verbal Learning (AVLT)	Diabetes	-.28*	.48**
	Age	-.30*	

Table 3: Relationships between clinical variables and NIH-TB cognitive indices.
Note: * p<.05; ** p<.01; *** p < .001;, # .05 > p < .10. Diabetes = History of type 2 diabetes, HbA1c = blood percentage of HbA1C, OSA = Obstructive Sleep Apnea history and/or current polysomonogram evidence; HTN = hypertension. For Symbol Coding and the AVLT, age was included as covariate along with sex, race, and years of education since age adjusted norms were unavailable for this NIH-TB measure.

DM diagnosis and current DM status (HbA1c) were the clinical factors most consistently with performance across most cognitive domains. Notably, BMI was only retained as significantly associated with performance in one cognitive domain (Attention: Flanker Task). The clinical factors found to be significantly associated with each relationships between clinical factors and performance on individual NIH-TB tasks are described below.

- **Card Sorting:** This measure of executive functioning involving set shifting was significantly associated with level of HbAIC (β=-.30, p<.01). Participants with elevated HbA1c had weaker Card Sorting performance.
- **Flanker Task:** The presence of two comorbidities (DM: (β=-.37, p<.001; BMI (β=-.25, p<.01) were significantly associated with weaker performance on task requiring spatial selective attention and executive control.
- **List Sorting:** Performance on this working memory task was associated with comorbid osteoarthritis (β=-.20, p<.05). Participants with osteoarthritis had greater difficulty with sequencing with a shorter span of stimuli that could be correctly sorted.
- **Pattern Comparison:** Performance on this processing speed measure was significantly associated with having comorbid DM (β=-.34, p<.05). Participants with DM were slower on this task requiring rapid responding.
- **Picture Sequencing**: Performance on this visual memory approached a significant associated with having comorbid DM (β=-.25, p<.10). Participants with DM tended to have weaker recall of picture sequences
- **Symbol Coding:** Performance on this coding task was associated with DM diagnosis and current status (R=.63, p<.001). Comorbid DM (β=-.50, p<.001) and elevated HbA1C (β=-.43, p<.01) were both associated with a slower rate of coding on this task that requires cognitive processing speed. Notably, age (β = -.50, p<.001) was also associated with performance on this task; slower coding with older age.
- **Verbal Learning:** Word recall across three trials on the AVLT was associated with comorbid DM (β=-.28, p<.05) and age (β=-.30, p<.05). Having comorbid DM and being older were associated with fewer words recalled.

Discussion

The results of this baseline analysis of NIH-TB neurocognitive indices from the WISE cohort study provides evidence in support of most of the original study hypotheses. Specifically, the findings indicate that: 1) Mild neurocognitive deficits exist among adults with severe obesity (Class II and Class III). These deficits are not ubiquitous, affecting some cognitive domains more than others; 2) Clinical comorbidities and risk factors associated with severe obesity appear to contribute to these deficits; and 3) The NIH-TB is sensitive to obesity-associated cognitive deficits, and to the relationship between specific comorbidities and these deficits.

Neurocognitive Deficits

Over 25% of participants in the cohort had a Fluid Cognition Composite score that was one or more standard deviations below normative expectations, with Fluid Cognition deficits occurring at about twice the predicted rate for a sample with a normal distribution (13%). In contrast, Crystalized Cognition for the cohort was at the 50th percentile. The rates of deficits on Oral Reading (6.5%) and Picture Vocabulary (8.9%), the two measures from the NIH-TB from which the Crystalized Cognition Composite score is derived was below expected levels. Also, the Crystalized Cognition Composite score was within one percentage point of BARONA-estimated premorbid verbal intellectual ability. The observed difference in rate of deficit between Fluid and Crystalized Cognition was expected given that functions subsumed under each. The constructs of fluid and crystalized cognition distinguishing between two broad categories of cognitive functions. Fluid cognition includes functions that require active ongoing processing of information for learning new information, reasoning, problem solving, and planning. From a neuropsychological perspective, attention, executive control, processing speed, working memory, and learning and recall are examples of Fluid Cognitive functions. Crystalized Cognition on the other hand is determined by the quantity and quality of stored information, knowledge and remote memory of past experiences and corresponds with verbal intellectual ability. Consistent with this distinction, deficits were evident on two NIH-TB tasks that contribute to the Fluid Cognition Composite score (Flanker and Patten Comparison) and two other tasks that require fluid cognition (Oral Symbol Coding, and Auditory Verbal Learning). The Flanker task is a widely studied attention paradigm that also requires executive control. Pattern Comparison requires rapid reaction time and cognitive processing speed. Oral Symbol Coding performance is also highly dependent on cognitive processing speed, but also requires working memory, sustained and focused attention, and memory encoding efficiency.

Fluid Cognition tends to be vulnerable to physiological state, and brain disorders that affect the speed and efficiency of cognitive processing; whereas, Crystalized Cognition is usually very stable, except when focal brain dysfunction exists with disruption of a specific functional neuroanatomic system (e.g., aphasia), or in the advanced stages of neurodegenerative disease. Obesity does not tend to directly cause focal brain disturbances or dementia, but rather contributes to metabolic disturbances, hemodynamic dysfunction, and sleep disorders, and other physiological alterations that can affect behavioral activity and energetics. Attention, executive functioning, working memory, and

cognitive processing speed are particularly vulnerable to these metabolic and physiological disturbances. While severe obesity increases the risk for stroke and AD with advanced age, which could impact Crystalized Cognition, these disorders are highly prevalent among adults with obesity.

Obesity-Associated Comorbidities

A primary question motivating the current study was whether excessive weight itself (i.e., elevated BMI) was the primary clinical factor underlying cognitive deficits among adults with severe obesity, or alternatively whether obesity-associated comorbidities play a key role. Given evidence from past studies of cognitive and brain dysfunction associated with DM, HTN and OSA, we hypothesized that these comorbidities would contribute to obesity-associated cognitive deficits. In particular, DM was hypothesized to be an important determinant of obesity-associated cognitive and brain dysfunction, as indicated by the title of the WISE Brain study, "Obesity and Type 2 Diabetes: Bariatric Effects on Brain Function". This hypothesis was supported, as DM was consistently and strongly associated with NIH-TB neurocognitive performance. DM diagnosis was the only comorbidity associated with Overall Cognition, and along with HTN, DM was associated with Fluid Cognition as well. DM diagnosis was also associated with performance on five of seven NIH-TB tasks (Flanker, Picture Sequencing, Pattern Comparison, Oral Symbol Coding and Verbal Learning), and HbA1c, an indicator of current DM status, was factor associated with Card Sorting performance. On only one cognitive task (List Sequencing) was DM diagnosis or HbA1c not implicated.

These findings from the WISE cohort are consistent with prior evidence of significant correlations between measures of glycemic control and cognitive performance in the LABS cohort [39]. In that study, pre-surgical baseline attentional switching and learning-memory performance were associated with DM diagnosis, HbAIC levels and also insulin resistance on the homeostasis model assessment (HOMA-IR). Notably, DM diagnosis and HbA1C levels had the strongest association with performance in these two cognitive domains, while HOMA-IR correlated moderately with only the memory composite score. The current results are also consistent with our past findings of significant associations of DM diagnosis and HbA1c levels with performance in the cognitive domains of attention, executive control, and processing speed as assessed by lengthier traditional neuropsychological assessment [40].

The pathophysiological bases for the adverse impact of DM on brain and cognition has received considerable investigation over the past two decades, including studies of DM as a risk factor for AD, with DM-associated metabolic disturbances possibly contributing to the underlying neurodegenerative mechanisms [41]. Brain dysfunction secondary to DM could occur as a byproduct of chronic insulin resistance, alterations in the liver-brain axis, the over- production of neurotoxic lipids (e.g., ceramides), and ultimately oxidative stress, and neuroinflammation. Endothelial damage also occurs as a result of chronic DM, alter vascular elasticity and integrity [42,43], increasing the risk for large vessel stroke, and also cerebral microvascular disturbances and the accumulation of white matter lesions [44,45]. All of these factors potentially contribute to the development of cognitive dysfunction, particularly as people age with chronic DM [46,47]. Severe obesity often leads to DM, which may contribute cognitive deficits. While results from the current study do not enable conclusions to be reached about whether these potential pathophysiological mechanisms are responsible, these findings strongly suggest that comorbid DM contributes to cognitive dysfunction in adults with severe obesity.

The lack of strong relationships between BMI and cognitive performance was somewhat surprising given that BMI is the defining characteristic of severe obesity, though not totally unexpected. Intuitively, a significant association between BMI and cognitive performance might be expected based on findings from past studies of an inverse relationship between BMI and cognitive functioning: i.e., higher BMI – weaker performance). Yet, elevated BMI was not significantly correlated with any cognitive measure in the LABS cohort [39], nor were associations found between BMI and performance across cognitive domains found in our past analysis neurocognitive functioning in adults with severe obesity [40]. So what accounts for this discrepancy? As discussed earlier, studies that have reported a significant relationship between BMI and cognition have tended to either examine risks associated with obesity from an epidemiological perspective in large populations, or reported on this finding based on analysis of cognitive data from community samples consisting of otherwise healthy adults. In these studies, the range of BMI typically was quite wide; from underweight to obesity. In contrast, the WISE and LABS cohorts, participants were exclusively adults with severe obesity. Besides consisting of only individuals with Class II and Class III obesity (a restricted range of BMI), the prevalence of comorbidities was quite high in these obesity-focused studies. Population-based studies on the other hand, have a lower prevalence of severe obesity and comorbidities; Class I obesity being relatively common, but a much lower proportion of Class II or III obesity. Such studies are very informative in showing the impact of elevated BMI in the context of the general population, but less are less useful for delineating the contribution of BMI and comorbidities of obesity to cognitive dysfunction among adults who are

severely obese. Accordingly, effects of BMI are likely diluted when studying participants with only Class II and III obesity, such that the influence of DM or other comorbidities is more pronounced. This does not diminish the adverse effected of having a very elevated BMI, as an increased prevalence of comorbidities are likely either a direct or indirect a manifestation of severe obesity.

While DM emerged as the comorbidity most strongly associated with cognitive deficits, the contribution of other comorbidities cannot be dismissed entirely. Hypertension diagnosis was associated with performance on the Fluid Cognition Composite score, but not with performance on any of the individual neurocognitive tasks. There is a large body of research linking hypertension to cognitive and brain dysfunction, though again this evidence tends to also come from epidemiological studies involving of large samples of the general population [24,48], or from studies focusing on the impact of uncontrolled hypertension [49,50]. Yet, clinical studies of cognitive functioning in the context of heart failure and other types of cardiovascular disease, often fail to find hypertension to be the major determinant of cognitive impairments [51]. This may reflect the fact that hypertension is relatively well controlled among patients with these diseases, and that other disturbances associated with severe cardiovascular disease play a greater role (e.g., cardiac output). While a history of hypertension was relatively common in the current cohort, most participants with hypertension were treated with medications and had relatively controlled blood pressures. Interestingly, osteoarthritis was associated with working memory performance on the List Sorting task, a finding that is somewhat difficult to explain. Perhaps increased inflammation associated with osteoarthritis affected working memory, though this was the only task on which this relationship was observed, and conclusions regarding the basis of this finding cannot be determined from the results of this study.

The results of this study have clinical implications for the cognitive assessment of adults with severe obesity, providing support for the validity of the NIH-TB as neurocognitive assessment approach. The NIH-TB was sensitive to both cognitive deficits, and also to the relationships between obesity-comorbidities and cognitive performance, with results that are consistent with past findings employing other assessment methods. The fact that the NIH-TB cognitive module can be administered in approximately 40 minutes makes it attractive and conducive to use in a clinical setting in which a comprehensive neuropsychological assessment is not feasible. Additional validation efforts are therefore warranted.

Several limitations exist regarding the conclusions that can be drawn from this study. This is a cross-sectional study of baseline cognitive functioning, so causality cannot be inferred. While medical record and detailed medical history data was available on all clinical measures, comorbidity diagnoses were coded categorically. For example, while OSA diagnosis was determined on the basis of medical record review, self-report, and polysomnogram results when feasible, a binary value was derived indicating the presence or absence of OSA. Also not participants had data from available from every data for purposes of adjudicating diagnostic category, which could have resulted in some imprecision. Data was not available regarding date of onset of medically diagnosed obesity, so that it was not possible to determine whether duration of obesity or its age of onset had any influence on the findings. It is also possible that other measures of obesity severity (e.g., body fat composition) may have proved to be more sensitive to cognitive performance than was BMI. Similarly, other measures of current DM status exist that also may have increased sensitivity to cognitive performance (e.g., fasting insulin, HOMA-IR). Unfortunately, these measures were not consistently available, as the laboratory data collected in the study was constrained in part by feasibility and whether they were standard clinical procedures for bariatric surgery patients at UF. There would be value in collecting these and other metabolic indices prospectively in future studies.

Summary and Conclusion

Compelling evidence of cognitive deficits among adults with severe obesity in the current study provides support for and extends past findings of a relationship between elevated BMI and reduced cognitive performance. The deficits observed in the study cohort were greatest with respect to executive functioning and cognitive processing speed relative to both normative data and pre-morbid intellectual abilities from estimated with the BARONA. As expected, comorbidities known to be common with severe obesity were in very prevalent in the study cohort. Most participants had at least one comorbid condition. Type-2 diabetes was the comorbidity most strongly and consistently associated with cognitive deficits in this cohort, while obstructive sleep apnea was the comorbidity associated with learning and memory performance. Counter to expectation, BMI was not significantly associated with overall cognitive performance or with deficits in most cognitive domains. This is probably attributable to the restricted range of BMI in this sample of adults with Class II and III obesity. None the less, this finding suggests that in the context of severe obesity, the presence of comorbidities such as diabetes takes on greater significance by adversely affecting cognitive functioning.

The current study is only one step towards disentangling these complex influences. While the association of diabetes or other comorbidities to cognitive deficits gives clues to possible underlying pathophysiological mechanisms,

other types of data are needed to adequately address these questions. Incorporating neuroimaging methods along with cognitive measures may help this effort. Multimodal neuroimaging is well suited in this regard, making it possible to simultaneously measure alterations in neural response of the brain with functional MRI, abnormal cerebral metabolite concentrations via magnetic resonance spectroscopy, reductions in cerebral blood flow using MRI methods such as arterial spin labeling, and the existence of neuroinflammation based on concentrations of extracellular free-water from diffusion imaging. As longitudinal data becomes available from the current study cohort following bariatric surgery, we will also be able to examine causal relationships to a greater extent by determining the relationship between improvements in BMI, diabetes status, and other comorbidities with changes in cognition. We will also examine changes that occur in the brain following bariatric surgery, analyzing data from multimodal neuroimaging relative to cognition.

Competing Interests

Dr. Cohen's work has been funded by the by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The authors declare no competing financial interests.

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