



Baseline associations between biomarkers, cognitive function, and self-regulation indices in the Cognitive and Self-regulatory Mechanisms of Obesity Study

Misty A.W. Hawkins¹  | Natalie G. Keirns¹  | Amanda N. Baraldi¹ | Harley M. Layman¹ | Madison E. Stout¹ | Caitlin E. Smith^{1,2} | John Gunstad³ | Deana A. Hildebrand⁴ | Kathleen D. Vohs⁵ | William R. Lovallo^{6,7}

¹Department of Psychology, Oklahoma State University, Stillwater, Oklahoma, USA

²Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

³Department of Psychological Sciences, Kent State University, Kent, Ohio, USA

⁴Department of Nutritional Sciences, Oklahoma State University, Stillwater, Oklahoma, USA

⁵Carlson School of Management, University of Minnesota, Minneapolis, Minnesota, USA

⁶Oklahoma City VA Medical Center, Oklahoma City, Oklahoma, USA

⁷Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

Correspondence

Misty A. W. Hawkins, Department of Psychology, 116 Psychology Building, Oklahoma State University, Stillwater, OK 74074, USA.

Email: misty.hawkins@okstate.edu

Funding information

National Heart, Lung, and Blood Institute, Grant/Award Number: F31HL152620; Oklahoma Shared Clinical and Translational Resources Center, Grant/Award Number: U5GM104938; CDC High Obesity Program and Diabetes and CVD Prevention program; National Institute of General Medical Sciences; National Institute of Aging, Grant/Award Number: R01AG065432; U.S. Department of Veterans Affairs; National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: K23DK103941; National Institute of Alcohol Abuse and Alcoholism, Grant/Award Number: AA12207; Center for Integrated Research on Childhood Adversity, Grant/Award Number: P20GM109097

Abstract

Objective: Understanding how biological, cognitive, and self-regulatory factors are related to obesity, and weight regulation is clearly needed to optimize obesity prevention and treatment. The objective of this investigation was to understand how baseline biological, cognitive, and self-regulatory factors are related to adiposity at the initiation of a behavioral weight loss intervention among treatment-seeking adults with overweight/obesity.

Methods: Participants ($N = 107$) in the Cognitive and Self-regulatory Mechanisms of Obesity Study (Identifier-NCT02786238) completed a baseline assessment with anthropometric, cardiometabolic, inflammatory, cognitive function, and self-regulation measures as part of a larger on-going trial. Data were analyzed with linear regression.

Results: At baseline, body mass index, body fat percentage, and waist circumference (WC) were positively associated with fasting insulin and insulin resistance. Higher WC was related to higher fasting glucose and hemoglobin A1c (HbA1c). Higher glucose and insulin resistance levels were related to lower list sorting working memory. Higher glucose and HbA1c levels were negatively associated with reading scores. Cognitive function and self-regulation indices were unrelated.

Conclusions: In adults with overweight/obesity entering a weight loss treatment study: (1) elevated WC and associated glycemic impairment were negatively

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. Obesity Science & Practice published by World Obesity and The Obesity Society and John Wiley & Sons Ltd.

associated with cognition, (2) poorer executive function and reading abilities were associated with poorer glycemic control, and (3) objectively measured cognitive functions were unrelated to self-reported/behavioral measures of self-regulation. Such findings increase understanding of the relationships between adiposity, biomarkers, cognition, and self-regulation at treatment initiation and may ultimately inform barriers to successful obesity treatment response.

KEYWORDS

biomarkers, cardiometabolic, cognition, glucose, self-regulation

1 | INTRODUCTION

Like many chronic cardiometabolic diseases, obesity is a complex, cyclical physiological process that impacts multiple organs, including the brain.¹ Excess adiposity is both a cause and consequence of cardiometabolic and inflammatory physiological changes (e.g., hypertension and insulin resistance)² that may burden neurocognitive functions.^{3,4} These impacts on neurocognitive function are seen at various levels of severity and scale—from relative, subclinical cognitive performance deficits at the behavioral level (e.g., impaired neuropsychological test performance)⁴ to increased risk of overt neurodegenerative disease (e.g., dementia) at a clinical level.³ Changes in structural and functional brain integrity are documented at all levels and across the lifespan.^{5,6}

Although the neurocognitive burden associated with obesity may be reversible with weight loss,⁷ this cognitive dysfunction may disrupt an individual's self-regulation efforts and contribute to the very obesity-promoting behaviors the individual may seek to avoid, such as excess calorie intake and sedentary behavior.^{8–10} For example, cognitive domains such as executive function have been shown to play a key role in participants' ability to adhere to behavioral treatment programs and their cognitive-behavioral targets.^{8–10} Emerging findings from basic and clinical obesity science have, thus, resulted in new conceptual frameworks “blaming the brain for obesity.”¹¹ Despite the growing emphasis on how obesity and its cardiometabolic sequelae relate to cognitive and brain function, no behavioral weight loss studies to date have examined all of the above factors concurrently in the context of obesity treatment to examine whether (1) dysregulation of certain biomarkers has more adverse effects than others, (2) certain cognitive domains are more impacted than others, or (3) particular cognitive functions map onto measures of self-regulation. Such studies may identify biopsychosocial and neurocognitive relationships that may ultimately prove to be important predictors of weight loss among those seeking obesity treatment.

This investigation takes a first step in addressing these gaps by examining the cross-sectional relationships between adiposity indicators and obesity-related biomarkers, cognitive function, and self-regulation indices among treatment-seeking adults with overweight/obesity. Each of these adults initiated a behavioral weight loss

program as part of the Cognitive and Self-regulatory Mechanisms of Obesity Study (COSMOS) trial.¹² This study presents results related to the first aim of the COSMOS trial, which is to examine the relationships between baseline obesity-related physiological dysregulation, cognitive deficits, and poor self-regulation.¹²

Each biomarker in COSMOS was selected for its previously documented associations between excess adiposity^{13–16} as well as a potential mechanistic role in adverse cognitive impacts.^{17–22} These biomarkers include indices of poorer glycemic control (e.g., hyperglycemia and insulin resistance) and cardiovascular function (e.g., high blood pressure or resting heart rate) as well as increased inflammatory markers (e.g., elevated cytokines, acute phase reactants). Cognitive function was also assessed using a comprehensive approach (i.e., a neuropsychological battery), as excess adiposity has been linked to deficits across multiple cognitive domains, such as memory, executive function, and processing speed.²⁰ Adiposity was estimated using multiple anthropometric indicators to determine whether observed relationships varied across commonly used approximations of excess body fat.²³ Finally, self-regulation was assessed via widely used self-report and behavioral indicators^{24–27} to ascertain whether cognitive performance would be associated with these theoretical constructs of goal-directed behavior in the context of obesity treatment.^{28,29} Together, these multifactorial constructs align with a proposed model¹² i.e., the foundation of the COSMOS trial that purports that (1) disruptions in physiology from excess fat harm cognitive function, (2) relative cognitive deficits then contribute to reduced self-regulation, and (3) ineffective self-regulation results in behaviors that promote or maintain obesity.

The hypotheses for the first COSMOS aim were that – at treatment initiation: (1) greater adiposity would be associated with greater physiological dysregulation across the biomarkers, (2) greater physiological dysregulation would be associated with relatively poorer cognitive performance across multiple domains, and (3) poorer cognitive performance would be associated with poorer self-regulation on standard assessments. No a priori assumptions were made regarding which indices would show the strongest relationships. Such findings should be useful in characterizing not only the levels of existing excess adiposity, physiological dysregulation, cognitive performance, and self-regulation among adults initiating

behavioral weight loss but also in documenting baseline interrelationships among these factors.

Ultimately, these descriptive findings will be extended in the context of weight loss treatment success, which correspond to other aims of the COSMOS trial, including examining pre- to post-treatment change in biomarkers, cognition, and self-regulation across two different behavioral weight loss programs. Valuable comparisons can then be made between observed cross-sectional patterns among physiology, cognitive function, and self-regulation at treatment initiation versus prospective changes in these factors across different behavioral weight loss treatments.

2 | METHOD

Data presented are from adults with overweight/obesity enrolled in the ongoing COSMOS trial. The COSMOS trial (ClinicalTrials.gov Identifier: NCT02786238) is a multi-cohort pilot trial designed to explore the potential cognitive and self-regulatory mechanisms of obesity and weight loss in two treatment groups of interest—acceptance-based and standard behavioral treatments. This paper presents the baseline associations of physical, cognitive, and self-regulation factors among trial participants at treatment initiation.

2.1 | Participants

Participants were adults with overweight/obesity recruited from the local university and community. Participants were included if they were aged between 21 and 65 years, spoke English, had a baseline BMI ≥ 27.0 and ≤ 52 kg/m². They were excluded if they did not meet inclusion criteria, had a physical or mental health reason that would make participation in the study difficult or dangerous (e.g., cancer, substance use, visual impairment, physical disability, and pregnancy), had or were pursuing bariatric surgery, were taking medications that might impact weight loss, or were currently enrolled in another weight loss program (WW®). Additional details regarding inclusion/exclusion criteria for the study can be found in the published protocol.¹² All participants provided written informed consent and were compensated. One hundred and eight participants (72% female, 24% marginalized racial group status) were enrolled. One participant was excluded from all analyses due to extreme values on fasting insulin (110.17 mIU/L) indicative of poorly controlled diabetes (Exclusion f).¹²

2.2 | Measures

2.2.1 | Adiposity measures

Multiple measures to estimate adiposity were collected, and all were measured in the laboratory by research personnel. Body weight (kg) and fat mass (kg) were measured with a research-grade

bioelectrical impedance analysis scale (Model TBF 310GS; Tanita Corporation). Body fat percent (BF%) was measured with the same device as the percent of fat mass/total body weight $\times 100$. Body mass index (BMI; kg/m²) was calculated. Waist circumference (WC; cm) was measured according to World Health Organization protocols.³⁰

2.2.2 | Additional Biomarkers

The following measurements were collected as biological indicators associated with obesity and/or neurocognitive function.

Metabolic indicators

Fasting glucose (mg/dl), fasting insulin (mIU/L), and hemoglobin A1c (HbA1c; %) were measured as metabolic indicators. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using fasting glucose and insulin values.³¹ Indicators were measured with blood samples separated into whole blood and plasma and analyzed using commercially available kits.

Cardiovascular indicators

Systolic (SBP) and diastolic (DBP) blood pressure (mmHg) and heart rate (HR; bpm) were measured according to American Heart Association³² guidelines using a professional-grade digital blood pressure monitor (Model HEM-907XL IntelliSense; OMRON). SBP, DBP, and HR values were calculated as an average of the last three of five total readings.

Inflammatory indicators

High-sensitivity c-reactive protein (hs-CRP; mg/dl), interleukin 6 (IL-6; pg/ml), and tumor necrosis factor (TNF- α ; pg/ml) were measured to assess systemic inflammation. Inflammatory indicators were measured with serum or plasma blood specimens. All analyses were performed at a certified laboratory using commercially available kits.

2.2.3 | Cognitive function

The NIH Toolbox Cognition Battery (NIHTB-CB)³³ and Automated Neuropsychological Assessment Metrics-IV (ANAM-IV)³⁴ were administered. The NIHTB-CB is a well-validated computerized cognitive test battery delivered via tablet and comprised of seven subtests: (1) Picture Vocabulary (language), (2) Oral Reading Recognition (language), (3) Picture Sequence Memory (episodic memory), (4) Flanker Inhibitory Control and Attention (inhibition/selective attention), (5) Dimensional Change Card Sort (cognitive flexibility), (6) List Sorting (working memory), and (7) Pattern Comparison Processing (processing speed).³³ These tests yield T-scores ($M = 50$, $SD = 10$) corrected for variation due to participants' age, gender, education, and race/ethnicity.³⁴ Two executive control tests (Go/No-Go Hits; % correct; 0–100 and Stroop Color-Word; number

correct) were utilized from the ANAM-IV, another computerized cognitive battery delivered via laptop.³⁴ To create a more parsimonious and comprehensive measure of executive function and to reduce multiple testing, a latent Executive Function/Speed variable was created using the two ANAM-IV tests and the following three NIHTB-CB tests: Flanker Inhibitory Control and Attention, Dimensional Change Card Sort, and Pattern Comparison Processing. All indicators have loaded together in previous factor analyses.³⁵ The following NIHTB-CB tests were modeled using observed single indicators and represent the working memory (List Sorting), episodic memory (Picture Sequence Memory), vocabulary (Picture Vocabulary), and reading (Oral Reading Recognition) domains. These single indicators have also been shown to be independent factors in previous studies.³⁵ For all indicators, higher scores indicate better cognitive performance.

2.2.4 | Self-regulation

For self-report measures, participants completed the Brief Self-Control Scale (BSCS)²⁴ and the Effortful Control Scale (ECS).²⁵ The 10-item BSCS measures trait self-control with good reliability and validity.²⁴ Cronbach's alpha for the present sample was 0.78. The ECS has two 12-item subscales that measure tendencies to persist (ECS-Control) and to inhibit impulses (ECS-Impulsivity) and also has good reliability and validity.²⁵ Alphas for the present study were 0.80 (Control) and 0.71 (Impulsivity). Two behavioral tasks were administered (i.e., the Handgrip Strength Test (HGT)²⁷ and an unsolvable puzzle²⁶); however, the unsolvable puzzle data were excluded from analyses due to an identified systematic error in administration. For the HGT, the time (seconds) that participants spent gripping a dynamometer at $\geq 70\%$ of their maximum grip (kg) was used. A latent Self-Regulation variable was calculated using BSCS total score, the two ECS subscales, and the HGT time as indicators. A higher score on all indicators was indicative of higher self-control except for the ECS-Control scale, in which higher scores indicate lower self-control.

2.2.5 | Demographic factors and key covariates

Self-report questionnaires were used to assess demographic factors (e.g., age [years], gender [0 = male, 1 = female], race-ethnicity [0 = white, 1 = marginalized racial group], education level [0 = did not complete high school, 1 = high school graduate, 2 = some college or Associates degree, 3 = Bachelors, and 4 = Masters, Professional, or Doctoral degree]). Weight history was measured with the Weight and Lifestyle Inventory. Psychosocial factors were measured via the following validated self-report instruments: Adverse Childhood Experiences Survey, Beck Depression Inventory-II, Emotional Eating Questionnaire-Revised, International Physical Activity Questionnaire, Philadelphia Mindfulness Scale, and the Power of Food Scale. See protocol for references.¹²

2.3 | Procedure

Upon study enrollment, participants completed a fasting blood draw at a nearby health center and an in-laboratory assessment. Following collection, blood samples were separated into serum or plasma, placed into sterile tubes, and refrigerated or frozen until analysis. Analyses were conducted at local-certified laboratories. The in-laboratory assessment was conducted by trained research personnel and included measurement of physical, psychosocial, and cognitive factors. After arriving, participants completed the NIHTB-CB and ANAM-IV tests. Second, participants' adiposity indicators and cardiovascular functioning were measured. Then, behavioral assessment of self-regulatory abilities was conducted. Participants were then given a packet of self-report measures of self-regulation, demographics, and covariates to return at their first treatment session. All study procedures were approved by the university's Institutional Review Board and are in line with APA ethical standards.

2.3.1 | Data analyses

After cleaning and error checking, data were analyzed using *Mplus* 8.3³⁶ using maximum likelihood estimation to include cases with missing data. First, correlations were run between the biomarkers, cognitive, and self-regulation variables to identify meaningful bivariate associations—with a focus on correlations of $r \geq |0.30|$ (moderate or greater magnitude). Then a series of regressions were conducted. Each model included gender, marginalized racial group status, and education as covariates as well as relevant auxiliary variables to support analyses with missing data³⁷ (e.g., BMI and WC for BF%, DBP for SBP, etc.). For the first set of models examining adiposity and physiological dysregulation, the three observed adiposity indicators were examined in separate models. All of the biomarkers (e.g., glucose, insulin, etc.) were regressed upon each adiposity indicator. The next set of regressions examined the relationship between biomarkers and cognitive function with each biomarker examined in a separate model with all latent and measured cognitive variables. The final set of regressions examined associations between the cognitive and self-regulation by regressing the latent self-regulation variable onto each cognitive variable in a separate model.

3 | RESULTS

Participants were predominantly white, highly educated, middle-aged females classified into the class II obesity category (see Table 1). WC was in the "high risk" range or greater category.³⁸ BF% values were in the category of elevated risk for metabolic syndrome.³⁹ Fasting glucose levels met the lower threshold of "pre-diabetes."⁴⁰ Fasting insulin levels were also elevated from standard cut-point, while HbA1c approached the clinical threshold.^{40,41} The HOMA-IR values also approached thresholds indicating insulin resistance.^{42,43} hs-CRP was elevated above the thresholds while IL-6 and TNF- α levels were within normal limits. Automated Neuropsychological Assessment

TABLE 1 Baseline characteristics of participants (N = 107)

Variables with units, range, and/or clinical thresholds	Total sample N (%) or M \pm SE ^a	% missing data; N
<i>Demographics</i>		
Age (years)	45.37 \pm 1.09	0.0; 0
Gender (female)	78 (73%)	0.0; 0
Marginalized racial group status (yes)	23 (22%)	2.8; 3
American Indian/Alaska Native	5 (4.7%)	-
Asian	2 (1.9%)	-
Black or African American	5 (4.7%)	-
Multiracial	6 (5.6%)	-
Other	5 (4.7%)	-
Education (\geq Bachelor's degree)	81 (76%)	1.9; 2
<i>Adiposity variables</i>		
Body mass index; BMI (kg/m ² ; 18.5–24.9 normal)	35.60 \pm 0.57	1.9; 2
Percent body fat (%; <29% for men and <37% for women)	41.45 \pm 0.70	1.9; 2
Waist circumference (cm; <102 cm for men; <88 cm for women)	107.31 \pm 1.25	1.9; 2
<i>Biomarkers</i>		
<i>Metabolic indices</i>		
Fasting glucose (mg/dl; <100 normal)	100.91 \pm 2.46	0.0; 0
Fasting insulin (mIU/L; <8.4 normal)	12.67 \pm 0.78	1.9; 2
HOMA-IR (mIU/L; <2.7 normal)	2.30 \pm 0.13	1.9; 2
HbA1C (%; <5.7 normal)	5.61 \pm 0.09	0.9; 1
<i>Cardiovascular indices</i>		
Systolic blood pressure (mmHg; <120 normal)	118.55 \pm 1.40	2.8; 3
Diastolic blood pressure (mmHg; <80 normal)	78.26 \pm 1.02	2.8; 3
Heart rate (bpm; 60–100 normal)	73.75 \pm 1.05	2.8; 3
<i>Inflammatory indices</i>		
hs-C-reactive protein; CRP (mg/L; <2.0 normal)	6.14 \pm 0.80	0.0; 0
Interleukin-6; IL-6 (pg/ml; <1.8 normal)	1.22 \pm 0.09	0.9; 1
Tumor necrosis factor; TNF-alpha (pg/ml; <5.6 normal)	2.22 \pm 0.06	0.9; 1
<i>Cognitive function</i>		
NIHTB-cognition battery (T-score M = 50, SD = 10; \leq 35 borderline impaired)		
Vocabulary	54.72 \pm 0.86	3.7; 4
Oral reading	56.16 \pm 0.85	3.7; 4
Processing speed	52.21 \pm 1.30	3.7; 4
Episodic memory	54.44 \pm 1.23	3.7; 4
Inhibitory control	40.28 \pm 0.69	3.7; 4
Cognitive flexibility	50.54 \pm 1.04	3.7; 4
Working memory	53.54 \pm 0.82	3.7; 4
ANAM-IV battery		
Go/No-Go Hits (% correct, 0–100)	94.85 \pm 0.18	1.9; 2
Stroop Task Color-Word (# correct)	36.38 \pm 1.15	2.8; 3

(Continues)

TABLE 1 (Continued)

Variables with units, range, and/or clinical thresholds	Total sample N (%) or M \pm SE ^a	% missing data; N
<i>Self-regulation indices</i> (possible range)		
Brief Self-control Scale (10–50)	34.42 \pm 0.62	12.1; 13 ^b
Effortful Control Scale–Control (1–5)	2.14 \pm 0.05	12.1; 13 ^b
Effortful Control Scale–Impulsivity (1–5)	3.65 \pm 0.05	12.1; 13 ^b
Hand-grip strength time (seconds)	18.98 \pm 1.61	1.9; 2

Abbreviations: ANAM-IV, Automated Neuropsychological Assessment Metric-IV; HOMA-IR, homeostatic model of insulin resistance; NIHTB; National Institutes of Health Toolbox; SE, standard errors.

^aMean and SE estimates calculated using full information maximum likelihood which utilizes all observed data to estimate parameters.

^bThe highest percent of missing was from the take-home survey packet given to participants to bring back to their treatment session, as some participants did not return their packets within the baseline period.

Metric regard to cardiovascular indices, participants were normotensive with resting HRs within normal limits.³² Scores on the neuropsychological tests were also within normal limits based on fully corrected T-scores and standard scores.^{33,34}

3.1 | Excess adiposity & dysregulation of biomarkers

Moderate correlations emerged between at least one marker of adiposity and the following biomarkers: fasting glucose and insulin, HOMA-IR, HbA1c, leptin, SBP, and hs-CRP (see Table 2). All associations, except for SBP, were robust to the addition of age, gender, race-ethnicity, and education in the multivariate models (see Table 3). Higher levels of all three adiposity indicators (BMI, BF%, and WC) were consistently related to higher fasting insulin and higher HOMA-IR values, whereas only the higher abdominal adiposity (WC) was associated with higher fasting glucose and HbA1c levels (Table 3). The amount of variance explained by greater adiposity across the metabolic variables ranged from 19% to 36%. Higher BMI and BF% were also associated with higher leptin (Table 3), accounting for 20%–22% of the variance. With regards to inflammatory markers, higher hs-CRP levels showed effect sizes of similar magnitude and direction but reached significance only for BF% (Table 3). Although bivariate associations were small-to-moderate ($r_s = 0.18$ – 0.26 ; Table 2), all three adiposity variables were also positively related to higher IL-6 in the multivariate models (Table 3). Across these two inflammatory indicators, greater adiposity accounted for 10%–13% of their variance.

3.2 | Dysregulation of biomarkers & cognitive performance

Moderate correlations emerged between at least one biomarker and the following cognitive function indices: reading, inhibitory control, working memory, and executive control (i.e., Stroop Color-Word) (see Table 2). After adjusting for demographics and education, significant associations remained such that higher glucose and HOMA-IR were

associated with lower list sorting working memory scores with glucose accounting for 17% of the variance in working memory scores and HOMA-IR accounting for 13% (see Table 4). Higher glucose and higher HbA1c levels were related to lower reading scores and accounted for 18% and 13% of the respective variances (Table 4). Higher IL-6 was associated with higher picture sequence episodic memory scores (7% of variance) while higher DBP was associated with higher vocabulary scores (10% of variance; Table 4).

Importantly, although no biomarkers were associated with the latent Executive function/Speed variable, some indicators (i.e., glucose and HbA1c) exhibited moderate bivariate correlations with certain individual tests comprising the latent score (i.e., processing speed, inhibitory control, and Stroop Color-Word) (Table 2). Thus, *post hoc* analyses of these individual tests were performed. In these models including demographic, education, and language/memory cognitive variables, higher glucose ($\beta = -0.32$, $p = 0.003$) and HbA1c ($\beta = -0.25$, $p = 0.027$) were associated with lower executive function scores as measured via Stroop Color-Word. In contrast, both higher glucose ($\beta = 0.22$, $p = 0.061$, trend) and HbA1c were associated with higher inhibitory control ($\beta = 0.28$, $p = 0.017$).

3.3 | Cognitive performance & self-regulation indices

No moderate correlations were detected between the individual cognitive function variables and self-regulation indices (results not shown for bivariate associations). Consistent with this pattern, in the multivariate models, no cognitive function variables were significantly associated with the self-regulation latent variable (all $p_s \geq 0.221$) (Table 5).

4 | DISCUSSION

The first hypothesis that greater adiposity would be associated with greater physiological dysregulation was supported in this sample with overweight/obesity. Greater excess weight, particularly higher

TABLE 2 Correlations between indicators of adiposity, biomarkers, and cognitive function

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
<i>Adiposity</i>																								
1. BMI	--																							
2. BF%	0.50	--																						
3. WC	0.76	0.09	--																					
<i>Biomarkers</i>																								
4. Fasting glucose	0.18	-0.09	0.33	--																				
5. Fasting insulin	0.45	0.14	0.56	0.54	--																			
6. HOMA-IR	0.35	0.04	0.46	0.44	0.78	--																		
7. HbA1C	0.14	-0.14	0.34	0.85	0.44	0.40	--																	
8. Leptin	0.21	0.43	0.01	-0.00	0.02	-0.02	-0.03	--																
9. Systolic BP	-0.11	-0.32	0.06	0.27	0.16	0.17	0.25	-0.18	--															
10. Diastolic BP	0.03	-0.06	0.08	0.05	0.15	0.14	0.03	-0.13	0.79	--														
11. Heart rate	0.10	0.08	0.00	0.16	0.28	0.33	0.14	-0.04	0.01	0.20	--													
12. hs-CRP	0.32	0.20	0.26	0.07	0.38	0.30	0.04	0.11	0.10	0.19	0.14	--												
13. IL-6	0.23	0.18	0.26	0.22	0.35	0.25	0.20	0.29	0.04	0.12	0.07	0.30	--											
14. TNF-alpha	0.01	-0.06	0.07	0.11	0.11	0.04	0.13	0.21	0.07	-0.06	-0.01	-0.11	0.13	--										
<i>Adiposity</i>																								
<i>Metabolic</i>												<i>Inflammatory</i>												
<i>Cognitive function</i>																								
15. Vocabulary	0.26	0.13	0.28	-0.00	0.04	-0.04	0.03	-0.06	0.14	0.25	-0.03	0.19	0.16	-0.14	--									
16. Oral reading	0.03	0.02	-0.03	-0.32	-0.10	-0.11	-0.26	-0.12	0.06	0.14	-0.10	0.14	0.03	-0.17	0.51	--								
17. Processing speed	-0.05	-0.03	-0.10	-0.20	-0.03	-0.03	-0.15	-0.01	-0.01	0.03	0.14	-0.04	0.07	0.18	0.07	0.10	--							
18. Episodic memory	-0.02	0.07	-0.03	-0.07	-0.03	-0.05	-0.03	-0.08	-0.00	0.07	0.09	0.14	0.22	-0.05	0.16	0.04	0.22	--						
19. Inhibitory control	0.17	-0.09	0.23	0.31	0.21	0.22	0.39	-0.08	0.15	0.04	0.04	0.12	0.08	-0.02	0.21	0.08	0.20	0.01	--					
20. Cog flexibility	-0.05	-0.06	-0.01	0.13	0.06	0.05	0.12	-0.04	0.05	-0.07	-0.05	-0.01	0.09	-0.04	0.18	0.05	0.35	-0.01	0.61	--				
21. Working memory	-0.02	-0.07	0.04	-0.32	-0.16	-0.21	-0.18	-0.08	-0.13	-0.08	-0.04	0.01	0.07	-0.03	0.25	0.22	0.20	0.26	0.04	0.04	--			
22. Go/No-Go Hits	-0.10	-0.12	-0.02	-0.11	-0.05	0.03	-0.04	-0.08	0.03	0.02	0.07	0.03	0.02	0.03	0.26	0.09	0.25	0.11	0.13	0.23	0.12	--		
23. Stroop C-W	0.12	0.06	0.08	-0.31	0.03	0.02	-0.24	-0.03	-0.05	0.10	0.02	0.12	0.20	-0.08	0.24	0.43	0.33	0.20	0.10	0.17	0.32	0.34	--	

Note: Correlations estimated using full information maximum likelihood.

Abbreviations: BF, body fat; BMI, body mass index; BP, blood pressure; C-W, color-word subtest; HbA1C, hemoglobin A1C; HOMA-IR, homeostatic model of insulin resistance; Hs-CRP, high sensitivity C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; WC, waist circumference.

TABLE 3 Regressing biomarkers on individual adiposity indicators adjusting for age, gender, marginalized racial group status, and education

Adiposity variables	BMI				BF%				WC			
	R ²	β	SE	p	R ²	β	SE	p	R ²	β	SE	p
<i>Biomarkers</i>												
<i>Metabolic</i>												
Glucose	0.27	0.28	0.16	0.086	0.25	0.20	0.19	0.288	0.30	0.38	0.15	0.013*
Insulin	0.29	0.51	0.10	<0.001*	0.23	0.58	0.14	<0.001*	0.36	0.60	0.09	<0.001*
HOMA-IR	0.23	0.46	0.12	<0.001*	0.19	0.57	0.15	<0.001*	0.28	0.55	0.12	<0.001*
HbA1C	0.25	0.29	0.17	0.084	0.22	0.20	0.20	0.318	0.29	0.41	0.17	0.013*
Leptin	0.22	0.25	0.10	0.012*	0.21	0.31	0.12	0.010*	0.20	0.17	0.12	0.158
<i>Cardiovascular</i>												
SBP	0.13	-0.14	0.09	0.113	0.14	-0.25	0.13	0.052	0.13	-0.10	0.10	0.340
DBP	0.07	0.01	0.10	0.894	0.07	0.04	0.15	0.790	0.07	0.04	0.10	0.681
HR	0.11	0.11	0.09	0.248	0.12	0.20	0.16	0.182	0.10	0.03	0.11	0.769
<i>Inflammatory</i>												
hs-CRP	0.12	0.28	0.16	0.071	0.10	0.32	0.16	0.043*	0.13	0.29	0.185	0.121
IL-6	0.10	0.26	0.11	0.020*	0.10	0.36	0.12	0.005*	0.14	0.35	0.091	<0.001*
TNF-alpha	0.01	0.03	0.10	0.750	0.01	-0.12	0.16	0.429	0.01	0.09	0.116	0.428

Note: Presented coefficients are the biomarkers simultaneously regressed on either BMI, BF%, or WC. Each adiposity variable was examined in a separate model with the other two adiposity indicators included as auxiliary variables. The following covariates were included in every model: age, gender, marginalized racial group status, and education. Significant coefficients are also bolded.

Abbreviations: BF, body fat; BMI, body mass index; C-reactive protein; DBP, diastolic blood pressure; HOMA-IR, homeostatic model of insulin resistance; Hs-CRP, high sensitivity; IL, interleukin; SBP, systolic blood pressure; SE, standard error; TNF, tumor necrosis factor; WC, waist circumference.

*Significant at $p < 0.05$.

central obesity measured via WC, was consistently related to higher fasting glucose and insulin levels, greater insulin resistance, and chronic hyperglycemia. Greater adiposity was also associated with elevated inflammatory markers, IL-6 and hs-CRP, as well as higher levels of the satiety hormone leptin. In contrast, none of the adiposity variables were associated with cardiovascular indices or TNF- α . The metabolic indicators most reliably associated with all excess weight indicators were fasting insulin and insulin resistance – although higher fasting glucose and HbA1c were associated with greater WC. IL-6 levels emerged as the inflammatory marker most consistently related to greater adiposity. Coefficients for hs-CRP were in a similar direction and magnitude across all adiposity indicators – though not always reaching statistical significance in this modest sample.

The finding that WC accounted for the highest levels of variance across the biomarkers is likely due to the close links that visceral fat displays with glucose-insulin homeostasis and diabetes onset,^{15,16} and evidence that WC independently predicts visceral fat over and above BMI.⁴⁴ Higher BMI also showed strong associations across the biomarkers, speaking to its ability to predict general obesity, particularly non-abdominal and abdominal subcutaneous fat independently of WC.⁴⁴ The study is also consistent with past work showing that IL-6 and hs-CRP may be more predictive of poor health outcomes than

TNF- α (e.g., these two inflammatory markers predicted mortality, whereas TNF- α did not).⁴⁵ Taken together, the findings align with previous evidence highlighting central obesity (particularly markers of visceral fat) as more strongly and consistently associated with physiological dysregulation (especially impaired glycemic control) compared to general obesity.²³ However, these results also support the recommendation that both central (e.g., WC) and general anthropometric (e.g., BMI) obesity variables can identify increased health risk from excess total, abdominal, and visceral fat,⁴⁴ such as elevations in inflammatory markers like IL-6 and hs-CRP.

The second hypothesis that greater physiological dysregulation would be associated with relatively poorer cognitive performance was supported, especially for certain biomarkers and cognitive domains. Elevated fasting glucose and insulin resistance were associated with lower working memory. Higher glucose and chronic hyperglycemia (i.e., HbA1c levels) were also related to lower reading scores, accounting for 13%–18% of the variance in cognitive scores, independent of demographics and education levels. Higher glucose and HbA1c were also associated with lower executive function scores as measured on the Stroop task, accounting for 16%–20% of the variance. These findings parallel to those found in other samples in which hyperglycemia, insulin resistance, and/or diabetes diagnosis

TABLE 4 Regressing neurocognitive domains on individual biomarkers adjusting for age, gender, marginalized racial group status, and education (N = 107)

Cognitive domain	Executive function/speed ^a			Working memory (List sorting)			Episodic memory (Picture sequence)			Language (Vocabulary)			Language (Reading)							
	R ²	β	SE	p	R ²	β	SE	p	R ²	β	SE	p	R ²	β	SE	p				
Biomarkers																				
Metabolic																				
Glucose ^b	0.08	0.06	0.14	0.666	0.17	-0.11	0.04	0.005*	0.03	-0.04	0.13	0.741	0.06	-0.08	0.13	0.506	0.18	-0.39	0.11	0.000*
Insulin	0.08	0.08	0.11	0.490	0.09	-0.15	0.11	0.163	0.03	-0.02	0.10	0.855	0.06	-0.03	0.11	0.803	0.07	-0.11	0.10	0.262
HOMA-IR	0.08	0.08	0.11	0.510	0.13	-0.25	0.10	0.011*	0.03	-0.06	0.11	0.551	0.06	-0.08	0.10	0.458	0.07	-0.11	0.10	0.288
HbA1C	0.08	0.10	0.15	0.488	0.11	-0.19	0.12	0.123	0.03	0.01	0.13	0.916	0.06	-0.02	0.13	0.887	0.13	-0.30	0.12	0.010*
Leptin	0.08	-0.07	0.11	0.563	0.07	-0.04	0.10	0.677	0.04	-0.13	0.10	0.209	0.06	-0.05	0.10	0.594	0.07	-0.14	0.10	0.166
Cardiovascular																				
SBP	0.08	-0.03	0.11	0.813	0.09	-0.14	0.10	0.157	0.03	0.05	0.10	0.649	0.07	0.11	0.10	0.264	0.07	0.11	0.10	0.290
DBP	0.09	-0.11	0.11	0.321	0.07	-0.06	0.10	0.537	0.03	0.10	0.10	0.317	0.10	0.21	0.10	0.029*	0.08	0.13	0.10	0.159
HR	0.07	0.01	0.11	0.942	0.09	-0.03	0.10	0.736	0.03	0.07	0.10	0.504	0.06	-0.06	0.10	0.584	0.07	-0.14	0.10	0.167
Inflammatory																				
hs-CRP	0.08	0.09	0.11	0.408	0.07	0.02	0.10	0.871	0.04	0.11	0.10	0.394	0.09	0.17	0.10	0.078	0.06	0.08	0.10	0.394
IL-6	0.10	0.16	0.11	0.131	0.09	0.13	0.10	0.203	0.07	0.21	0.10	0.027*	0.08	0.16	0.10	0.107	0.06	0.01	0.10	0.884
TNF-alpha	0.07	-0.01	0.11	0.856	0.07	-0.03	0.10	0.777	0.03	-0.04	0.10	0.647	0.08	-0.14	0.09	0.147	0.08	-0.17	0.09	0.070

Note: Each biomarker is a separate model. All models included the following covariates: age, gender, marginalized racial group status, education. All cognitive variables were included in each model. Significant coefficients are also bolded.

Abbreviations: DBP, diastolic blood pressure; HOMA-IR, homeostatic model of insulin resistance; HR, heart rate; Hs-CRP, high sensitivity; IL, interleukin; SBP, systolic blood pressure; SE, standard error; TNF, tumor necrosis factor.

^aThe Executive Function/Speed variable is a latent variable comprised of the following individual tests: Flanker Inhibitory Control, Card Sort Test, Stroop Color-Word, Go/No-Go Hits, and Pattern Processing Speed.

^bDue to convergence issues using full information maximum likelihood with missing covariates, these results are from N = 104.

*p < 0.05.

TABLE 5 Regressing self-regulation on individual cognitive function indicators adjusting for age, gender, marginalized racial group status, and education (N = 107)

Cognitive domain	Self-regulation ^a			
	R ²	β	SE	p
Executive function/speed ^b	0.21	-0.16	0.13	0.236
Working memory-List sorting	0.18	-0.01	0.06	0.887
Episodic memory-Picture sequence	0.19	0.03	0.11	0.301
Language-vocabulary	0.21	-0.13	0.11	0.221
Language-reading	0.20	-0.05	0.06	0.342

Note: Each cognitive function variable is a separate model.

^aThe Self-regulation variable is a latent variable comprised of the following tests: Brief Self-Control Scale, Effortful Control Subtests, and Handgrip Strength Test.

^bThe Executive Function/Speed variable is a latent variable comprised of the following tests: Flanker Inhibitory Control, Card Sort Test, Stroop Color-Word, Go/No-Go Hits, and Pattern Processing Speed.

*p < 0.05.

were the most prominent clinical comorbidities linked to greater cognitive dysfunction.²¹ Of note, contradictory results are also available in the literature. For example, average HbA1c was not associated with cognitive function over 7 years of follow-up.⁴⁶ However, the Beavers and colleagues' sample was adults with overweight or obesity who had already developed type 2 diabetes mellitus, which could indicate that chronic hyperglycemia no longer exerts unique detriment to cognition once diabetes severity reaches clinical thresholds.⁴⁶ Future studies that allow comparisons with healthy participants (i.e., those with no excess weight or diabetes diagnosis such as Reppel et al.²²), will be essential for clarifying the true nature of these associations across the spectrum of weight as well as metabolic and inflammatory health. Notably, Reppel and colleagues did find evidence that subclinical HbA1c elevations below the diagnostic threshold for diabetes were related to both cognitive performance and white matter integrity in their sample of over 1200 healthy, young adults.²²

Interestingly, the observed patterns of glycemic and cognitive impairment were reversed for another measure of executive function in the present study sample, with higher scores on the Flanker Inhibitory Control test related to higher glucose and HbA1c. These effects were unexpected and may be an artifact of this measure's performance in this particular sample. Specifically – despite the present sample being highly educated with “average to high-average scores” on the majority of the cognitive tests—scores on the Flanker Inhibitory Control test stood out as the lowest. These scores were the only ones that were markedly “low average” using cognitive benchmarks and had the least variability, suggesting not only relative deficits on this measure (consistent with meta-analytic findings),⁴⁷ but also potential restricted range. Thus, these positive correlations and coefficients should likely be interpreted with caution. Relatedly, higher IL-6 and DBP levels were associated with better episodic memory and vocabulary scores, respectively, in this sample. Given the lack of theoretical basis, the absence of a clear and consistent

pattern for these markers, and the high number of models examined, these effects may be spurious; however, additional studies should clarify these suppositions.

The final hypothesis that poorer cognitive performance would be associated with poorer self-regulation was not supported. While unexpected theoretically and complicated by the higher levels of missing data on the self-report measures, this finding is not the first time that self-reported self-regulation measures have been unrelated to cognitive testing of self-control.⁴⁸ In their meta-analysis of five datasets with over 2600 participants, Saunders et al.⁴⁸ also found that the Self-Control Scale, the most widely used measure of self-reported self-control, was not correlated with the Flanker Inhibitory Control or Stroop tests. One of the studies in their report even found a small negative association, which is consistent with the direction of the non-significant beta coefficients observed between the self-regulation latent score and the majority of the cognitive variables in the present investigation. Saunders et al. concluded that these patterns of findings do not invalidate either approach to measuring self-regulation capacity but merely highlight that cognitive tests of executive function are not analogous to the self-report measures of self-control and vice versa.⁴⁸ Additionally, self-regulation measures like the Self-Control Scale may be more weakly associated with eating and weight behaviors than with other behavioral domains like school or work, suggesting that there is heterogeneity in how well self-report measures of self-regulation actually predict certain behaviors.⁴⁹ Together, these inconsistencies highlight the complexities of self-regulation assessment and also call for continued multimodal assessment of the construct, particularly in the context of eating, obesity, and weight loss.^{48,49}

The mechanistic pathways underlying the study findings are numerous. Specifically, as excess weight accumulates in the body, particularly in the abdominal cavity and around vital organs (i.e., visceral fat), impairments in glucose and lipid metabolism increase.^{15,16} These gluco-regulatory and lipid disturbances are associated with the sequelae of other negative outcomes that have been proposed to result in the poor cognitive performance observed in the present study and others, including but not limited to: impaired transport of glucose across the blood brain barrier, abnormalities in endothelial function, vasodilation and other vascular abnormalities, reduced acetylcholine availability, liver-brain axis alterations that produce toxic lipid and ceramide levels, increased neuro-inflammation, low levels of brain-derived neurotrophic factor, axonal degeneration, white matter lesions, and hippocampal atrophy.^{21,50-56}

In addition to obesity-related biological changes, an individual's excess adiposity levels do not exist independently of the larger social determinants of health. These determinants act together to impact not only obesity development and progression but may also exert their own independent influences on cognitive function. For instance, economic instability and poverty are critical barriers to healthy food access, and persons at socioeconomic disadvantage have greater exposure to highly processed food-like substances and less access to fresh produce (e.g., food swamps and deserts).⁵⁷ Unfortunately, low cost diets high in refined sugars and fats may have independent negative effects on

central appetite control and cognitive function that can be observed prior to obesity onset.⁵⁸⁻⁶⁰ Then, the built environment and neighborhoods in which people live can determine whether they have viable options for safe exercise.^{61,62} The evidence linking exercise with better cognitive health is well-established,⁶³ so environments that foster more sedentary behavior may have cognitive costs or deny cognitive benefits. Finally, discrimination is another established social determinant of physical health—with emerging support that it is also cognitively taxing. Weight stigma may not only be obesity-promoting via its association with psychological stress and cortisol secretion,⁶⁴ it may also be responsible, in part, for the cognitive deficits observed in persons with obesity.⁶⁵ Future studies need to disentangle the unique contributions of obesity as a biological state from the physiological and psychological threats invoked by socioeconomic factors and discrimination to determine their relative contributions to cognitive function. In sum, clear biological, psychological, and social pathways are implicated in the obesity-cognition relationship.¹⁰

Although this study's strengths included a comprehensive assessment of various markers of adiposity, a diverse array of cardiometabolic and inflammatory indicators, multiple cognitive domains, and self-regulation measures, a key limitation should be noted. Namely, all relationships between these baseline variables are cross-sectional, and directionality cannot be established. This limitation is particularly important for biomarker-cognition relationships. Although the current work primarily presents excess adiposity and corresponding physiological dysregulation as a driver of cognitive deficits, poorer cognitive abilities may also plausibly drive physiological decline, either as etiological or maintaining factors.⁶⁶ For example, poorer crystallized cognitive ability (i.e., language/reading) may contribute to lower health literacy or non-adherence to complex medical regimens.⁶⁷ Likewise, poorer fluid abilities (e.g., executive functions, processing speed) may inhibit sustained engagement in goal-directed health behaviors related to weight loss.⁸⁻¹⁰ Such factors then contribute to a feedback loop in which cognitive deficits yield greater adiposity over time.⁶⁸ Future work coming from this ongoing study may help clarify some of these temporal relationships – though better-powered prospective studies are still needed.

In sum, these results suggest that – among an adult sample with existing excess adiposity: (1) elevated adiposity, particularly WC, and associated glycemic impairment have the greatest adverse impacts on cognition, (2) poorer executive function and reading abilities are most closely implicated with poorer glycemic control, and (3) objectively measured cognitive functions do not readily map onto self-reported or behavioral measures of self-regulation abilities in the context of weight regulation. These conclusions can be used to guide future studies on cardiometabolic factors and brain health by encouraging more precise estimations of fat type and distribution, ensuring that markers of glycemic control be prioritized, including both fluid and crystallized cognitive measures, and not assuming that self-report and cognitive testing indices of self-control are equivalent. These steps should aid in better understanding of factors linking adiposity, biomarkers, cognition, and self-regulation to develop optimal intervention options for those with excess weight.

Evaluations of whether these factors predict treatment response will also help determine their potential roles as moderators and/or mechanisms of weight change in behavioral obesity treatments, an upcoming goal of the ongoing COSMOS study.

ACKNOWLEDGEMENTS

This project was directly supported by the National Institute of Diabetes and Digestive and Kidney Disease (K23DK103941 to Misty A.W. Hawkins). Misty A.W. Hawkins was also supported by the Center for Integrated Research on Child Adversity (CIRCA; P20GM109097) funded by the National Institute of General Medical Sciences and by the Oklahoma Shared Clinical Translational Resources Center (OSCTR; U5GM104938). Natalie G. Keirns was supported by a National Heart, Lung, and Blood Institute training award (NHLBI; F31HL152620). John Gunstad was supported by the National Institute on Aging (R01AG065432). Deana Hildebrand was supported under a CDC High Obesity Program and Diabetes and CVD Prevention program funds. William R. Lovallo was supported by the Department of Veterans Affairs and the NIAAA (AA12207).

As PI of the trial, Misty A.W. Hawkins conceived and supervised implementation of the trial protocol, reporting of results, and completed the first manuscript draft; Natalie G. Keirns, Harley M. Layman, Madison E. Stout, and Caitlin E. Smith were trial interventionists, assessors, data managers, and helped to coordinate the trial; Amanda N. Baraldi provided statistical consultation and conducted analyses; John Gunstad provided expert consultation of neuropsychological testing and data; Deana Hildebrand provided expert consultation on nutritional content; Kathleen D. Vohs provided expert consultation on self-regulation indices; and William R. Lovallo provided expert consultation on biomarkers and analyses. All authors were involved in writing and editing the paper and had final approval of the submitted and published versions. Thanks are also due to Larry Mullins, Joel Hughes, and Doug Delahanty who were co-mentors on the initial K23 application. We also give sincere thanks to our trial participants—without their participation and support, no study would be possible.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ORCID

Misty A.W. Hawkins  <https://orcid.org/0000-0002-3825-639X>

Natalie G. Keirns  <https://orcid.org/0000-0002-1455-7964>

REFERENCES

1. Stice E, Burger K. Neural vulnerability factors for obesity. *Clin Psychol Rev.* 2019;68:38-53.
2. Rochette AD, Spitznagel MB, Strain G, et al. Mild cognitive impairment is prevalent in persons with severe obesity. *Obesity.* 2016; 24(7):1427-1429.
3. Beydoun MA, Beydoun H, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev.* 2008;9(3):204-218.

4. Gunstad J, Lhotsky A, Wendell CR, Ferrucci L, Zonderman AB. Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology*. 2010;34(4):222-229.
5. Devoto F, Zapparoli L, Bonandrini R, et al. Hungry brains: a meta-analytical review of brain activation imaging studies on food perception and appetite in obese individuals. *Neurosci Biobehav Rev*. 2018;94:271-285.
6. Rothmund Y, Preuschhof C, Bohner G, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage*. 2007;37(2):410-421.
7. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2017;72:87-94.
8. Butryn ML, Martinelli MK, Rimmert JE, et al. Executive functioning as a predictor of weight loss and physical activity outcomes. *Ann Behav Med*. 2019;53(10):909-917.
9. Manasse SM, Flack D, Dochat C, Zhang F, Butryn ML, Forman EM. Not so fast: the impact of impulsivity on weight loss varies by treatment type. *Appetite*. 2017;113:193-199.
10. Gunstad J, Sanborn V, Hawkins M. Cognitive dysfunction is a risk factor for overeating and obesity. *Am Psychol*. 2020;75(2):219-234.
11. Berthoud H-R, Münzberg H, Morrison CD. Blaming the brain for obesity: integration of hedonic and homeostatic mechanisms. *Gastroenterology*. 2017;152(7):1728-1738.
12. Hawkins MA, Colaizzi J, Gunstad J, et al. Cognitive and Self-regulatory Mechanisms of Obesity Study (COSMOS): study protocol for a randomized controlled weight loss trial examining change in biomarkers, cognition, and self-regulation across two behavioral treatments. *Contemp Clin Trials*. 2018;66:20-27.
13. Mouton AJ, Li X, Hall ME, Hall JE. Obesity, hypertension, and cardiac dysfunction: novel roles of immunometabolism in macrophage activation and inflammation. *Circ Res*. 2020;126(6):789-806.
14. Wu H, Ballantyne CM. Metabolic inflammation and insulin resistance in obesity. *Circ Res*. 2020;126(11):1549-1564.
15. Chartrand D, Larose E, Poirier P, et al. Visceral adiposity and liver fat as mediators of the association between cardiorespiratory fitness and plasma glucose/insulin homeostasis. *Am J Physiol Endocrinol Metab*. 2020;319(3):E548-E556.
16. Hanley A, Wagenknecht L, Norris J, et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family study. *Diabetologia*. 2009;52(10):2079-2086.
17. Nguyen JC, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci*. 2014;8:375.
18. Ekblad LL, Rinne JO, Puukka P, et al. Insulin resistance predicts cognitive decline: an 11-year follow-up of a nationally representative adult population sample. *Diabetes Care*. 2017;40(6):751-758.
19. Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. *Curr Hypertens Rep*. 2017;19(3):24.
20. Morys F, Dadar M, Dagher A. *Obesity Impairs Cognitive Function via Metabolic Syndrome and Cerebrovascular Disease: An SEM Analysis in 15,000 Adults from the UK Biobank*. bioRxiv; 2020.
21. Fernando HJ, Cohen RA, Gullett JM, et al. Neurocognitive deficits in a cohort with class 2 and class 3 obesity: contributions of type 2 diabetes and other comorbidities. *Obesity*. 2019;27(7):1099-1106.
22. Repple J, Karliczek G, Meinert S, et al. Variation of HbA1c affects cognition and white matter microstructure in healthy, young adults. *Mol Psychiatry*. 2019;26(4):1399-1408.
23. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. *Eur J Clin Nutr*. 2010;64(1):16-22.
24. Tangney JP, Baumeister RF, Boone AL. High self-control predicts good adjustment, less pathology, better grades, and interpersonal success. *J Pers*. 2004;72(2):271-324.
25. Lonigan CJ, Vasey MW. Negative affectivity, effortful control, and attention to threat-relevant stimuli. *J Abnorm Child Psychol*. 2009;37(3):387-399.
26. McFarlin DB, Baumeister RF, Blascovich J. On knowing when to quit: task failure, self-esteem, advice, and nonproductive persistence. *J Pers*. 1984;52(2):138-155.
27. Muraven M, Tice DM, Baumeister RF. Self-control as a limited resource: regulatory depletion patterns. *J Pers Soc Psychol*. 1998;74(3):774-789.
28. Teixeira PJ, Carraça EV, Marques MM, et al. Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. *BMC Med*. 2015;13(1):1-16.
29. Dohle S, Diel K, Hofmann W. Executive functions and the self-regulation of eating behavior: a review. *Appetite*. 2018;124:4-9.
30. World Health Organization. *Waist Circumference and Waist-hip Ratio: Report of a WHO Expert Consultation*. 8–11 December 2008. Geneva; 2011.
31. Uo Oxford. HOMA2 calculator. In: *Diabetes Trials Unit*. Oxford, UK: University of Oxford; 2013.
32. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension*. 2019;73(5):e35-e66.
33. Weintraub S, Dikmen SS, Heaton RK, et al. Cognitive assessment using the NIH Toolbox. *Neurology*. 2013;80(11 Supplement 3):S54-S64.
34. Kane RL, Reeves DL. Computerized test batteries. *Neuropsychology Handb*. 1997;1:423-467.
35. Mungas D, Heaton R, Tulskey D, et al. Factor structure, convergent validity, and discriminant validity of the NIH Toolbox Cognitive Health Battery (NIHTB-CHB) in adults. *J Int Neuropsychol Soc*. 2014;20(6):579-587.
36. Muthén LK, Muthén BO. 1998–2012. *Mplus User's Guide*. Los Angeles: Muthen & Muthen; 2012.
37. Enders CK. A note on the use of missing auxiliary variables in full information maximum likelihood-based structural equation models. *Struct Equ Model A Multidisciplinary Journal*. 2008;15(3):434-448.
38. NHLBI Obesity Education Initiative. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. Silver Spring, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, NHLBI Obesity Education Initiative, North American Association for the Study of Obesity; 2000.
39. Zhu S, Wang Z, Shen W, Heymsfield SB, Heshka S. Percentage body fat ranges associated with metabolic syndrome risk: results based on the third National Health and Nutrition Examination Survey (1988–1994). *Am J Clin Nutr*. 2003;78(2):228-235.
40. American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care*. 2017;40(Supplement 1):S11-S24.
41. Johnson J, Duick D, Chui M, Aldasouqi S. Identifying prediabetes using fasting insulin levels. *Endocr Pract*. 2010;16(1):47-52.
42. Geloneze B, Vasques ACJ, Stabe CFC, et al. HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). *Arquivos Brasileiros de Endocrinol Metabologia*. 2009;53:281-287.
43. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419.
44. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *Am J Clin Nutr*. 2002;75(4):683-688.

45. Giovannini S, Onder G, Liperoti R, et al. Interleukin-6, C-reactive protein, and tumor necrosis factor- α as predictors of mortality in frail, community-living elderly individuals. *J Am Geriatrics Soc*. 2011;59(9):1679-1685.
46. Beavers KM, Leng I, Rapp SR, et al. Effects of longitudinal glucose exposure on cognitive and physical function: results from the action for health in diabetes movement and memory study. *J Am Geriatrics Soc*. 2017;65(1):137-145.
47. Lavagnino L, Arnone D, Cao B, Soares JC, Selvaraj S. Inhibitory control in obesity and binge eating disorder: a systematic review and meta-analysis of neurocognitive and neuroimaging studies. *Neurosci Biobehav Rev*. 2016;68:714-726.
48. Saunders B, Milyavskaya M, Etz A, Randles D, Inzlicht M. Reported self-control is not meaningfully associated with inhibition-related executive function: a Bayesian analysis. *Collabra Psychol*. 2018;4(1):39.
49. De Ridder DT, Lensvelt-Mulders G, Finkenauer C, Stok FM, Baumeister RF. Taking stock of self-control: a meta-analysis of how trait self-control relates to a wide range of behaviors. *Pers Soc Psychol Rev*. 2012;16(1):76-99.
50. Lamport DJ, Lawton CL, Mansfield MW, Dye L. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. *Neurosci Biobehav Rev*. 2009;33(3):394-413.
51. Suzanne M. Insulin resistance and Alzheimer's disease. *BMB Rep*. 2009;42(8):475.
52. Wang M, Norman JE, Srinivasan VJ, Rutledge JC. Metabolic, inflammatory, and microvascular determinants of white matter disease and cognitive decline. *Am J Neurodegener Dis*. 2016;5(5):171.
53. Cohen RA, Paul RH, Ott BR, et al. The relationship of subcortical MRI hyperintensities and brain volume to cognitive function in vascular dementia. *J Int Neuropsychol Soc*. 2002;8(6):743-752.
54. Mielke MM, Haughey NJ, Bandaru VVR, et al. Plasma ceramides are altered in mild cognitive impairment and predict cognitive decline and hippocampal volume loss. *Alzheimer's Dementia*. 2010;6(5):378-385.
55. Iriondo A, García-Sebastian M, Arrospide A, et al. Plasma lipids are associated with white matter microstructural changes and axonal degeneration. *Brain Imaging Behav*. 2020;15(2):1-15.
56. Krabbe K, Nielsen A, Krogh-Madsen R, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia*. 2007;50(2):431-438.
57. Cooksey-Stowers K, Schwartz MB, Brownell KD. Food swamps predict obesity rates better than food deserts in the United States. *Int J Environ Res Public Health*. 2017;14(11):1366.
58. Lowette K, Roosen L, Tack J, Vanden Berghe P. Effects of high-fructose diets on central appetite signaling and cognitive function. *Front Nutr*. 2015;2:5.
59. Barnes JN, Joyner MJ. Sugar highs and lows: the impact of diet on cognitive function. *J Physiol*. 2012;590(12):2831.
60. Hawkins MA, Keirns NG, Helms Z. Carbohydrates and cognitive function. *Curr Opin Clin Nutr Metab Care*. 2018;21(4):302-307.
61. Gordon-Larsen P, Nelson MC, Page P, Popkin BM. Inequality in the built environment underlies key health disparities in physical activity and obesity. *Pediatrics*. 2006;117(2):417-424.
62. Kärmeniemi M, Lankila T, Ikäheimo T, Koivumaa-Honkanen H, Korpelainen R. The built environment as a determinant of physical activity: a systematic review of longitudinal studies and natural experiments. *Ann Behav Med*. 2018;52(3):239-251.
63. de Asteasu MLS, Martinez-Velilla N, Zambom-Ferraresi F, Casas-Herrero A, Izquierdo M. Role of physical exercise on cognitive function in healthy older adults: a systematic review of randomized clinical trials. *Ageing Res Rev*. 2017;37:117-134.
64. Himmelstein MS, Incollingo Belsky AC, Tomiyama AJ. The weight of stigma: cortisol reactivity to manipulated weight stigma. *Obesity*. 2015;23(2):368-374.
65. Guardabassi V, Tomasetto C. Weight status or weight stigma? Obesity stereotypes—not excess weight—reduce working memory in school-aged children. *J Exp Child Psychol*. 2020;189:104706.
66. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev*. 2011;12(9):740-755.
67. Wolf MS, Curtis LM, Wilson EA, et al. Literacy, cognitive function, and health: results of the LitCog study. *J Gen Intern Med*. 2012;27(10):1300-1307.
68. Hawkins MA, Gunstad J. Body weight and neurocognition function. In: Brownell KD, Walsh BT, eds. *Eating Disorders and Obesity: A Comprehensive Handbook*. New York, NY: Guilford Publications; 2017:84-88.

How to cite this article: Hawkins MAW, Keirns NG, Baraldi AN, et al. Baseline associations between biomarkers, cognitive function, and self-regulation indices in the Cognitive and Self-regulatory Mechanisms of Obesity Study. *Obes Sci Pract*. 2021;7(6):669-681. <https://doi.org/10.1002/osp4.537>