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ORIGINAL ARTICLE

Pediatric Obesity

Differences in adolescent cerebral perfusion as a function of obesity: Results from the FLEX-Brain study

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Abstract

Objective: Children and adolescents have greater resting cerebral blood flow (rCBF) during periods of rapid brain growth. Overweight and obesity have a global impact on brain cerebrovascular health in adults, but whether these effects are discernable in adolescents with overweight and obesity remains unknown. This study examined differences in rCBF between adolescents with a healthy weight (HW) and adolescents with overweight or obesity (OW).

Methods: The current study focused on analyzing data from 58 participants (mean age = 15.43 [SD 1.37] years). Participants were classified into OW (n = 38) and HW groups (n = 20) according to the Centers for Disease Control and Prevention's guidelines for children. Voxelwise t tests between the HW and OW groups were conducted to test for regional group differences in rCBF, controlling for age and sex. Mean rCBF was extracted from a gray matter mask to compare global rCBF between the HW and OW groups.

Results: The HW group had greater rCBF compared with the OW group in five clusters, with peaks in the cerebellum, precentral gyrus, and supplementary motor area. No clusters survived correction for the OW > HW contrast. Global rCBF did not significantly differ between the groups (p = 0.09).

Conclusions: These results suggest that overweight and obesity in adolescence are associated with discernable reductions in blood flow to specific brain regions rather than having a global impact on rCBF.

INTRODUCTION

It is estimated that 14.4 million children in the United States have a BMI that qualifies as obesity (1). According to the Centers for Disease Control and Prevention, children have an overweight BMI if it is at or above the 85th percentile based on their age and sex (2). Obesity is defined as having BMI at or above the 95th percentile compared with peers of the same age and sex (2). Child and adolescent obesity is associated with an increased risk for several comorbidities, including type 2 diabetes, insulin resistance, and hypertension (3-5). Given these trends, there is a need to better understand how pediatric obesity relates to brain function.

Childhood and adolescence are critical periods for brain development. Childhood obesity has been linked to alterations in brain function across the life-span (6). Resting cerebral blood flow (rCBF), one of the most fundamental aspects of brain function, measures blood flow throughout the brain, which provides information about how the brain meets and regulates metabolic demand (7). As the brain undergoes rapid growth in youth, a closer examination of rCBF can provide insight into how the brain constructs, energizes,

and organizes the additional brain matter (8). Children and adolescents have greater rCBF during periods of rapid brain growth (8). Overweight and obesity have a global impact on brain cerebrovascular health in adults (9,10), but whether these effects are discernable in children and adolescents with overweight or obesity remains unknown. Overweight and obesity may lead to reduced rCBF in youth, as in adults, because excess weight is associated with damage to the cardiovascular and cerebrovascular systems (11).

The current study aimed to examine differences in rCBF between adolescents with a healthy weight (HW) and adolescents with overweight or obesity (OW). Based on prior research, we predicted that the HW group would have greater rCBF compared with the OW group in prefrontal brain regions, as these regions undergo some of the most extensive development during adolescence (12,13). Further, we predicted that the HW group would have greater global rCBF compared with the OW group.

Study Importance

What is already known?

- Children and adolescents have greater resting cerebral blood flow (rCBF) during periods of rapid brain growth.
- Overweight and obesity have a global impact on brain cerebrovascular health in adults, but whether these effects are discernable in adolescents with overweight and obesity remains unknown.

What does this study add?

- The healthy weight (HW) group had greater rCBF compared with the overweight/obesity group (OW) group in five clusters, with peaks in the cerebellum, precentral gyrus, and supplementary motor area.
- The OW group did not have greater rCBF compared with the HW group in any clusters.
- Global rCBF did not differ between the HW and OW groups.

How might these results change the direction of research or the focus of clinical practice?

- These results may suggest that overweight and obesity in adolescence are associated with discernable reductions in blood flow to specific brain regions rather than having a global impact on rCBF.
- These findings highlight the importance of weight within the context of pediatric brain development to reduce the risk for decreased rCBF.

METHODS

Participants

Sixty participants were recruited to take part in a 6-month healthy lifestyle intervention at the University of Pittsburgh called Fun, Lifestyle, Exercise, and the Brain (FLEX-Brain; NIH R56HL128317; PI: Rofey). Participants completed a baseline neuroimaging session that included a pseudo-continuous arterial spin labeling (pcASL) scan to measure rCBF. Only the baseline rCBF data were used for this analysis. Participants were considered eligible if they met all of the following criteria: 12 to 17 years of age; postpubertal (i.e., Tanner Stage IV-V determined using the Pubertal Development Scale); and involvement of at least one caregiver. Participants were excluded if they met any of the following criteria: pregnancy, breastfeeding, or planning a pregnancy within the next 6 months; history of bariatric surgery; medical condition affecting body weight, including cancer, diabetes mellitus, hyperthyroidism, renal insufficiency, liver disease, and gastrointestinal disorders; heart problems, uncontrolled arrhythmia, or cardiovascular disease, including uncontrolled hypertension; eating disorder that could contraindicate weight loss; psychotropic medication use; suicide attempt within the last year; metal in the body; claustrophobia; documented traumatic brain injury requiring medical treatment; neurological disorder, including epilepsy, autism spectrum disorder, and narcolepsy; and BMI < 5th percentile for youth who are underweight. Participants with BMI ≥ 85th percentile were assigned to the OW group, and participants with BMI < 85th percentile were assigned to the HW group. One participant did not have neuroimaging data available and one participant's rCBF data were removed because of poor quality. Therefore, the current study focused on analyzing the baseline data of 58 participants from the FLEX-Brain sample. Data for race and caregiver education were missing for 24% of the full sample, consisting of 10% for the HW group and 31.6% for the OW group. This study was approved by the institutional review board, and parents and participants provided written informed consent.

Magnetic resonance imaging

Acquisition

All magnetic resonance images were acquired with a Siemens 3.0-T scanner (Magnetom Trio Tim Syngo, Munich, Germany). A 32-channel phased-array head coil was used for radio frequency (RF) transmission and reception. Foam padding was positioned within the head coil to minimize participant motion. High-resolution T1-weighted anatomical images were acquired for coregistration with the following sequence parameters: magnetization prepared rapid acquisition of gradient echo (MPRAGE), matrix = 256, field-of-view = 250 mm, voxel size = 1.0 × 1.0 × 1.0 mm, sections = 192 (sagittal plane, acquired left to right), section thickness = 1.0 mm, repetition time (TR) = 1,900 milliseconds, echo time (TE) = 2.93 milliseconds, inversion time = 900 milliseconds, flip angle = 9°, and sequence duration = 4:26 minutes. In order to quantify rCBF, we employed pcASL, a perfusion-weighted magnetic resonance imaging (MRI) technique. Perfusion-weighted images were collected at

rest using a multisection pcASL protocol for perfusion quantification with the following parameters (14): matrix size = 64, field-of-view = 220 mm, voxel size = 3.40 × 3.40 × 5.0 mm, sections = 20 (axial plane, acquired in ascending order), section thickness = 5.0 mm, gap between sections = 1 mm, single section acquisition time = 48 milliseconds, label duration = 1,500 milliseconds, post-label delay = 1,500 milliseconds, TR/TE = 4,090/21 milliseconds, volumes = 80, number of label/control pairs = 40, flip angle = 90°, RF blocks = 80, RF pulses = 20, gap between pulses = 360 microseconds, bandwidth = 2,298 Hz/pixel, and sequence duration = 5:35 minutes.

Preprocessing

The time series was coregistered with the T1-weighted anatomy using FMRIB's Software Library version 5.0.9 (FSL) Linear Image Registration Tool (FLIRT) (15,16). The time series was subsequently visually inspected for proper alignment. Partial volume estimates were derived from the T1-weighted anatomy using FMRIB's Automated Segmentation Tool (FAST) (17). These high-resolution tissue-type maps were used for partial volume correction, nuisance signal regression, and tissue-specific perfusion quantification.

Perfusion quantification

FSL's Bayesian Inference for Arterial Spin Labeling MRI (BASIL) toolbox was used for perfusion quantification (18). First, a rCBF image was generated from the coregistered time series using pairwise tag-control subtraction (asl_file). The images were adjusted for section-time delay. In order to further control for spurious signals, BASIL's oxford_asl command was run with the partial volume and spatial correction options turned on (19,20). The cerebral spinal fluid image from FAST was designated as the tissue reference for nuisance regression. This step also corrected the proton density image to adjust for potential errors in the blood-brain partition coefficient and applied a ventricular mask to the corrected image to isolate and compute the magnetization equilibrium (M0) of the white and gray matter tissue. The M0 value was used to approximate the M0 of the arterial blood and convert the relative rCBF values into absolute units of milliliters per 100 g per minute (asl_calib). Finally, the calibrated images were normalized to the standard space of the Montreal Neurological Institute (MNI) template. This resulted in a baseline rCBF map for each participant. Baseline rCBF images from each person were combined into a single four-dimensional file for group-level statistical analyses.

Analyses

For comparison between the HW and OW groups on key demographic characteristics at baseline, independent samples *t* tests were conducted. Independent samples *t* tests were also conducted between male and female participants on key demographic characteristics at baseline. Our primary aim was to test for regional group differences in rCBF. Voxelwise *t* tests between the HW and OW groups were conducted in FSL, in which the rCBF images were entered as the dependent variable. Randomise, a permutation-based algorithm, was used to accommodate parametric and nonparametric data (21). Two contrasts were produced: 1) HW > OW and 2) OW > HW. Age and sex were included as covariates in all models. A sensitivity analysis was performed with handedness included as an additional covariate. Results were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) at $p < 0.05$. TFCE is a statistical approach for addressing multiple comparisons of neuroimaging data without having to specify arbitrary cluster sizes and define clusters in a binary way. Our secondary aim was to test whether there was a difference in global rCBF between the HW and OW groups. In order to test this aim, mean rCBF was extracted from a gray matter brain mask. We then compared global rCBF between the HW and OW groups using an independent samples *t* test in SPSS Statistics version 25 (IBM Corp., Armonk, New York).

TABLE 1 Characteristics of the sample

	Total sample	HW group	OW group	*t*	*p* value
N	58	20	38		
Age, y (mean ± SD)	15.43 ± 1.37	15.69 ± 1.23	15.29 ± 1.44	−1.05	0.30
Sex (% female)	79.3	85.0	76.3	0.77	0.45
Handedness (% right-handed)	93.1	100	89.5	2.09	0.04
Caregiver Education (% ≤high school graduation)*	5.2	0	7.9	−1.81	0.08
Race (% Caucasian)*	55.2	75	44.7	−1.37	0.18
Tanner Stage	4.48	4.50	4.47	−0.19	0.85
BMI, percentile (mean ± SD)	82.17 ± 24.58	55.55 ± 25.42	96.18 ± 3.82	7.11	<0.001

For comparison between the HW and the OW groups on key demographic characteristics at baseline, independent samples *t* tests were conducted.

* Missing for two participants in the HW group and twelve participants in the OW group.

RESULTS

Characteristics of the sample

The participants were on average 15.43 years old (SD 1.37). Female participants made up 79.3% of the sample, and 93.1% of the sample was right-handed. Average BMI was in the healthy range (82nd percentile), consisting of 20 participants with a healthy BMI (<85th percentile) and 38 participants with a BMI classifying them as having overweight or obesity (≥85th percentile). Age, caregiver education, race, BMI, and Tanner Stage did not differ significantly between male and female participants ($p > 0.07$). There were no significant differences between the HW and OW groups for age, sex, race, caregiver education, or Tanner Stage (all $p > 0.08$), as shown in Table 1. Handedness significantly differed between groups ($t = 2.09$, $p = 0.04$) and, as expected, BMI significantly differed between groups ($t = 7.11$, $p < 0.001$).

TABLE 2 Peak coordinates of clusters showing greater rCBF for the HW group compared with the OW group

Cluster	Region	*k*	MNI x, y, z	*p* value
1	Cerebellum	888	31, 34, 6	0.02
2	Precentral gyrus	213	53, 50, 69	0.03
3	Supplementary motor area	151	51, 67, 65	0.03
4	Precentral gyrus	35	41, 52, 68	0.03
5	Cerebellum	3	63, 30, 14	0.05

k = cluster size.

Difference in perfusion

Voxelwise *t* tests between the HW and OW groups were conducted using TFCE at $p < 0.05$. The HW group had greater rCBF compared with the OW group in five clusters across the brain, with peaks located in the cerebellum ($k = 888$; peak MNI x, y, z = 31, 34, 6), precentral gyrus ($k = 213$; peak MNI x, y, z = 53, 50, 69), supplementary motor area ($k = 151$; peak MNI x, y, z = 51, 67, 65), precentral gyrus ($k = 35$; peak MNI x, y, z = 41, 52, 68), and cerebellum ($k = 3$; peak MNI x, y, z = 63, 30, 14) (Table 2; Figure 1). The results were unchanged when including handedness as a covariate in the model. When examining regions that showed greater rCBF for the OW group compared with the HW group (OW > HW contrast), no clusters survived TFCE correction for multiple comparisons. Global rCBF did not differ between the HW (66.10 [10.25]) and OW (61.45 [9.61]) groups ($t = -1.71$, $p = 0.09$).

DISCUSSION

Prior research has suggested that overweight and obesity in adulthood are associated with regional reductions in rCBF in the prefrontal cortex (22). Based on this literature, we predicted that the HW group would have greater rCBF compared with the OW group in prefrontal brain regions, as these regions undergo some of the most extensive development during adolescence (12,13). Broadly consistent with our hypothesis, our analyses revealed that the OW group had regionally specific reductions in rCBF in the cerebellum, precentral gyrus, and supplementary motor area compared with the HW group. These results are consistent with prior literature on adults that has

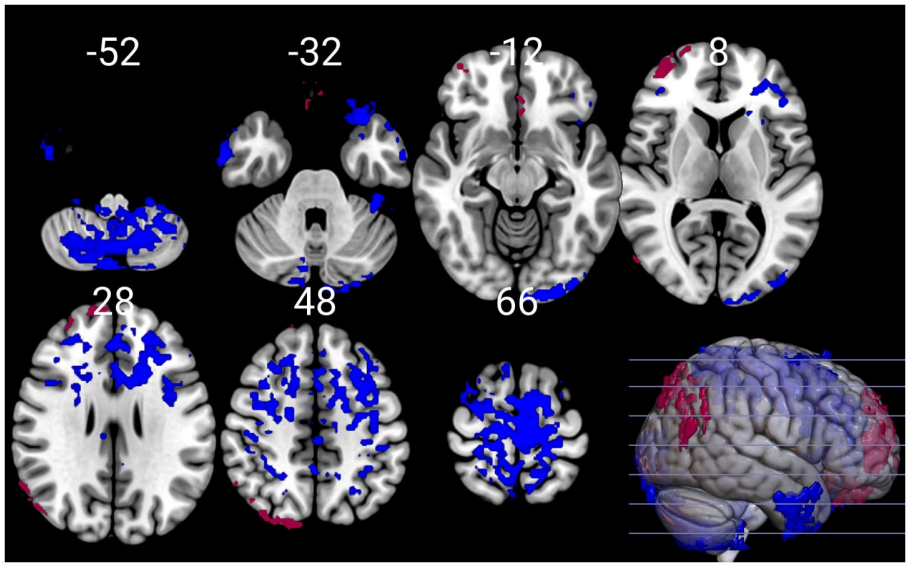

FIGURE 1 Cerebral blood flow differences between weight groups. The healthy weight group had greater cerebral blood flow compared with the overweight group in several clusters across the brain, with peaks located in the cerebellum, precentral gyrus, and supplementary motor area.

demonstrated that elevated BMI is associated with significant reductions in rCBF in the cerebellum, precentral gyrus, and supplementary motor area (10,22). Inconsistent with our hypothesis, our analyses also revealed that global rCBF did not significantly differ between groups. This is inconsistent with prior literature on adults with overweight and obesity (9,22), and may suggest that overweight and obesity in childhood and adolescence is associated with discernable reductions in blood flow to specific regions of the brain rather than having a global impact on rCBF.

Primary analyses revealed that the HW group had greater rCBF compared with the OW group in several regions, including the cerebellum, precentral gyrus, and supplementary motor area. These regions are implicated in motor function, including balance, motor sequencing, and motor control (23,24). Further, this regional specificity is in line with the results of previous neuroimaging studies that have observed that the cerebellum plays a prominent role in higher cognitive and emotional functions during childhood and adolescence, functions that are compromised in obesity (23). In addition, the cerebellum is thought to be particularly vulnerable to environmental influences (25) and is frequently implicated in childhood-onset disorders such as autism, dyslexia, and attention-deficit/hyperactivity disorder (26-28). Our results are consistent with prior literature that has demonstrated that obesity in childhood is associated with reduced gray matter volume in the cerebellum (29). The precentral gyrus has been implicated in response inhibition in youths (30,31) and has been found to be vulnerable to early-life stress (32). Finally, the supplementary motor area supports motor planning, learning, and execution (24). Our results are in line with prior literature that has demonstrated that adolescents with overweight and obesity have reduced seed-based connectivity between the insula and the supplementary motor area (33). Taken together, these results suggest that overweight and obesity in childhood and adolescence may have detrimental effects on rCBF and other metrics of brain health in regions that support higher cognitive and emotional functions, as well as motor functions.

Secondary analyses revealed that rCBF did not significantly differ globally across the brain between groups, although it approached significance (p = 0.09). However, studies with larger sample sizes might have greater power to detect a significant association for the entire cortex. Our results are inconsistent with the notion that obesity has a global impact on brain cerebrovascular health in adults (9). However, our results are consistent with studies that have shown regional changes in rCBF throughout brain development, particularly in the precentral gyrus (34,35). These results, coupled with the regional specificity of our findings, suggest that pediatric obesity may have detrimental effects on metabolic activity in distinct regions of the developing brain rather than having a global impact.

One potential mechanism for the observed reductions in rCBF associated with obesity is blunted cerebrovascular reactivity. Specifically, obesity is associated with respiratory distress and may lead to blunted arterial carbon dioxide receptor responses due to chronic stimulation (36). As a result, there may be a reduction in cerebral blood flow. Another mechanism that has been proposed is inward cerebral artery remodeling, such that the ability of vessels to dilate and contract is lost, and blood flow is dramatically affected (9). In obese rats, the ability to match blood flow to the regional metabolic demands of active neurons is impaired, which is dependent on the capacity of arterioles to dilate (9). Although the reasons, mechanisms, and behavioral implications of these regional differences remain unknown, it is possible that one or more of these mechanisms is occurring in children and adolescents with overweight and obesity. The results of the current study should be interpreted in the context of several limitations. Arterial spin labeling is among the noisiest of MRI modalities, and there are a number of alternative preprocessing pipelines that exist to minimize blood-oxygen-level-dependent signal noise, which may change the perfusion values slightly (37,38). However, the acquisition noise is expected to be constant across groups when using the same procedures and scanner, minimizing the influence of variability in preprocessing pipelines on the values we report. As with all cross-sectional studies, it is not possible to draw causal relationships from these findings. However, our results are consistent with those of longitudinal studies that have found that obesity is associated with an increased rate of vascular brain injury and decreased integrity of neural structures, as well as randomized controlled trials that have found that behavioral interventions can modify weight-related reductions in rCBF (39-41). Behavioral measures were not collected, limiting our ability to examine the behavioral implications of these results. Without being able to examine the link between rCBF and behavioral outcomes, we cannot conclude whether greater rCBF in the HW group is associated with healthy brain functioning. Further, although we can only speculate as to the underlying causes of the observed associations, our results provide insight into how pediatric obesity might influence an important measure of brain health. Additionally, given the small sample size, the results may be more robust with a larger sample size. Another limitation of this study is the disparity in missing data for race and caregiver education between the HW and OW groups, which may have limited our ability to detect a significant effect of these demographic variables on our outcomes of interest, thus potentially limiting the generalizability of the findings. Moreover, this sample was homogenous in regards to socioeconomic status, limiting the generalizability of these findings to other socioeconomic conditions. Finally, although the small number of male participants in this study limits our ability to examine sex differences, there was no evidence that they differ on other characteristics, including age, caregiver education, race, and BMI. Our novel sample of adolescents with overweight and obesity allows us to characterize these associations prior to adulthood. This is especially important, as previous rCBF studies are mostly comprised of adults despite the regional changes in rCBF observed throughout brain development (34,35). This study adds to a large body of extant literature on adults by examining rCBF in youth, whose brains undergo dramatic remodeling during childhood and adolescence.

CONCLUSION

We used advanced neuroimaging techniques to examine whether adolescent obesity was associated with rCBF. We demonstrated that overweight and obesity in adolescence is associated with regionally specific reductions in rCBF in the cerebellum, precentral gyrus, and supplementary motor area. These results have public health implications, highlighting the importance of weight within the context of pediatric brain development to reduce the risk for decreased rCBF. Our future research will examine whether a weight loss intervention in adolescents results in changes to rCBF.O

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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