

Associations Among Body Mass Index, Cortical Thickness, and Executive Function in Children

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IMPORTANCE A total of 25.7 million children in the United States are classified as overweight or obese. Obesity is associated with deficits in executive function, which may contribute to poor dietary decision-making. Less is known about the associations between being overweight or obese and brain development.

OBJECTIVE To examine whether body mass index (BMI) is associated with thickness of the cerebral cortex and whether cortical thickness mediates the association between BMI and executive function in children.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study, cortical thickness maps were derived from T1-weighted structural magnetic resonance images of a large, diverse sample of 9- and 10-year-old children from 21 US sites. List sorting, flanker, matrix reasoning, and Wisconsin card sorting tasks were used to assess executive function.

MAIN OUTCOMES AND MEASURES A 10-fold nested cross-validation general linear model was used to assess mean cortical thickness from BMI across cortical brain regions. Associations between BMI and executive function were explored with Pearson partial correlations. Mediation analysis examined whether mean prefrontal cortex thickness mediated the association between BMI and executive function.

RESULTS Among 3190 individuals (mean [SD] age, 10.0 [0.61] years; 1627 [51.0%] male), those with higher BMI exhibited lower cortical thickness. Eighteen cortical regions were significantly inversely associated with BMI. The greatest correlations were observed in the prefrontal cortex. The BMI was inversely correlated with dimensional card sorting ($r = -0.088$, $P < .001$), list sorting ($r = -0.061$, $P < .003$), and matrix reasoning ($r = -0.095$, $P < .001$) but not the flanker task. Mean prefrontal cortex thickness mediated the association between BMI and list sorting (mean [SE] indirect effect, 0.014 [0.008]; 95% CI, 0.001-0.031) but not the matrix reasoning or card sorting task.

CONCLUSIONS AND RELEVANCE These results suggest that BMI is associated with prefrontal cortex development and diminished executive functions, such as working memory.

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A total of 13.7 million children in the United States younger than 18 years are obese, and an additional 12 million children are classified as overweight.¹ The percentage of extreme obesity among children has continued to increase in the past decade and is now estimated to be approximately 750 000, or 6%, of children who meet the diagnostic threshold for obesity.² The negative metabolic and cardiovascular sequelae of increasing adiposity, obesity, and chronic obesity in children is well established. Children with obesity are more likely to develop early-onset type 2 diabetes and heart disease,³⁻⁵ tend to have more severe risk factors and disease burden,⁶ and are at greater risk for premature mortality than their healthy weight peers.^{7,8}

Higher body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) has also been

associated with poorer cognitive performance across the lifespan, particularly in the domain of higher executive functions.⁹⁻¹² Less is known about the effects of obesity and being overweight on brain development and how this might interact with cognitive ability. Many neuroimaging studies¹³⁻¹⁶ have found structural alterations in cortical regions involved in executive control in obese children compared with lean children. However, limited sample sizes, insufficient statistical power, differences in sample populations, and differing magnetic resonance imaging (MRI) modalities have yielded mixed results. Maayan et al¹³ reported that obese children performed worse on working memory tasks compared with healthy control individuals and had less orbitofrontal cortical volume, a brain region associated with appetite control. By contrast, Saute et al¹⁴ found an association between

increased visceral adiposity, but not BMI, and cortical thickness in a range of cortical regions outside the orbitofrontal cortex, and Sharkey et al¹⁵ found no statistically significant association between BMI and cortical thickness in healthy children 12 to 18 years of age.

Strong evidence supports metabolic dysregulation and dysfunction associated with escalating levels of adiposity. Chronic cellular stress and excessive inflammatory mediators in concert with extracellular adipocyte remodeling¹⁷ related to excessive adiposity are early pathophysiologic changes that lead to insulin resistance and thus cerebral and cardiovascular structural alterations.¹⁸ Neuroimaging studies have observed lower gray matter volume in association with increasing levels of adiposity in otherwise healthy individuals¹⁹ during the transition from childhood to early adolescence, a critical developmental period for brain development.²⁰ Metabolic aberrations early in life may hamper optimal brain development and maturation, which, in turn, may affect key areas of cognition early in life. Thus, our working hypothesis was that children with increasing levels of adiposity (ie, BMI) have a thinner cortex than do children who are leaner and that this alteration mediates executive functioning.

To clarify the association among cortical thickness, cognition, and adiposity in children, we examined a large sample of 9- and 10-year-old children from the Adolescent Brain Cognitive Development (ABCD). The aims of the study were to (1) evaluate regional associations between BMI and cortical thickness, (2) assess whether higher BMI was associated with lower executive functioning, and (3) examine whether cortical thickness in brain regions associated with BMI mediated the association between BMI and executive functioning.

Methods

Data Source

This cross-sectional study used data from the ABCD study, which was designed to examine the association of brain development with childhood experiences and examine how these experiences are associated with social, emotional, and physical health; the development of risky behaviors; and substance use prospectively. A large cohort of 9- and 10-year-old children were recruited at 21 US sites in 2017.²¹ Children were extensively assessed with regard to mental health, cognitive function, and social, cultural, and physical environments. The assessments included structural and functional MRI using a standardized multisite protocol. Analyses were conducted on data from the ABCD study's first (1.0) curated release, which included deidentified data from 4524 children aged 9 to 10 years. The local institutional review boards at each consortium site were responsible for ensuring protection of human subjects in accordance with the Declaration of Helsinki.²² Parents provided written informed consent, and children provided verbal assent.

Design and Sample

The study design, sample stratification, recruitment, and data collection procedures are detailed elsewhere.²³ Exclusion criteria for the ABCD study included moderate to severe intel-

Key Points

Question Is body mass index associated with cortical thickness in 9- and 10-year-old children, and does this association interact with executive functioning?

Findings In this cross-sectional study, higher body mass index was associated with thinner cortex, especially in the prefrontal cortex. The association between body mass index and working memory was partially mediated by prefrontal cortex thickness.

Meaning These findings suggest that body mass index is associated with cortical development and diminished executive functions, such as working memory.

lectual disability; current substance use disorder; noncorrectable vision, hearing, or sensorimotor impairments; major neurologic disorders; gestational age younger than 28 weeks; birth weight less than 1.2 kg; birth complications requiring more than 1 month of hospitalization; history of traumatic brain injury; and standard MRI contraindications (eg, implanted metals, claustrophobia, and orthodonture).²³ In addition, we excluded children with a current or past diagnosis of attention-deficit/hyperactivity disorder, any neurologic condition (eg, seizures, head injury, and/or cerebral palsy), diabetes type 1 or type 2, lead exposure, muscular dystrophy, schizophrenia, autism spectrum disorder, and a BMI less than 10. Only individuals with complete data on relevant variables and assessments were included in the analysis.

Nonimaging Measures

Body Mass Index

Heights and weights were objectively measured with individuals in light clothing. The BMI percentiles for age and sex were used to classify individuals as underweight (ie, <5%), within acceptable limits (ie, 5%-85%), overweight (ie, 85%-95%), and obese (ie, ≥95%).²⁴

Pubertal Status

Child pubertal status was assessed subjectively by parent report. Parents' rating of child physical development yielded a categorical maturation score similar to that of Tanner staging. Scores ranged from prepubertal (score of 1) to postpubertal (score of 5).²⁵

Cognitive Battery

The National Institutes of Health Toolbox Cognition Battery²⁶ evaluates cognitive domains of memory, language, and other higher-order executive processes. This study focused on measures of higher executive functions dependent on the prefrontal cortex. The flanker, dimensional Wisconsin card sorting, and list sorting working memory tasks assessed cognitive control and working memory. The matrix reasoning task, a subtest of the Weschler Intelligence Test for Children-V,²⁷ assessed fluid intelligence. Raw scores were corrected for age to yield a final age-corrected score. All instruments were administered and completed by individuals in 1 visit. A comprehensive overview of the ABCD cognitive battery can be found in the article by Luciana et al.²⁸

Structural Neuroimaging

Imaging Protocol

Structural MRI was performed at 21 sites in the United States using a standardized protocol²⁹ for imaging acquisition, processing, reconstruction, and quality control. All structural MRI findings were screened for incidental findings by a neuroradiologist.

Acquisition Parameters

Whole brain coverage was achieved using isotropic voxel resolution of $1 \times 1 \times 1$ mm, 256×256 matrix, flip angle of 8° , inversion delay of 1060 milliseconds, 176 to 225 sections, field of view of 256×240 to 256, field of view phase of 93.75% to 100%, repetition time of 2400 to 2500 milliseconds, echo time of 2 to 2.9 milliseconds, and parallel imaging of 1.5×2.2 . The total acquisition time was 5 minutes 38 seconds to 7 minutes 12 seconds.

Image Reconstruction

Structural MRIs were generated from T1-weighted and T2-weighted images that were processed and corrected for gradient nonlinearity distortions to ensure reliability across multiple imaging sites.³⁰ T2-weighted images were volume registered to T1-weighted images by adjusting and maximizing the relative position and orientation of mutual information among images.³¹ Intensity nonuniformity correction was based on tissue segmentation and sparse spatial smoothing. Images were resampled with 1-mm isotropic voxels into rigid alignment within the brain atlas. Cortical reconstruction and volumetric segmentation were performed using FreeSurfer software, version 5.3.0 (Harvard University). Images were stripped of skull and nonbrain material³² followed by white matter segmentation and initial mesh creation.³³ Correction of topologic defects followed procedures described by Fischl et al³⁴ and Ségonne et al.³⁵ Images underwent surface optimization³⁶⁻³⁸ and nonlinear registration to a spherical surface-based atlas.³⁹ Cortical regions were parcellated and labeled with a surface-based atlas classification that provides brain region of interest-level results that are easily replicable and freely available within the data release.⁴⁰

Quality Control

Protocol adherence was performed among imaging sites to ensure integrity and completeness.⁴¹ Images were manually reviewed for data quality. Images with the most severe artifact, irregularities, and/or poor image quality were rejected and excluded from processing and analysis. Cortical surface reconstruction images were reviewed for motion, intensity inhomogeneity, white matter underestimation, pial overestimation, magnetic susceptibility artifact, and susceptibility artifact.

Statistical Analysis

The analytic approach tested the model that higher levels of BMI (ie, adiposity) is associated with alteration of the integrity of the cortex and that these changes within the cortex are associated with impairments within the domains of executive functioning.

Regional Associations Between BMI and Cortical Thickness

A general linear model (GLM) was used to examine associations between BMI and mean cortical thickness in each of the 66 cortical brain regions parcellated according to the Desikan-Killiany atlas.⁴⁰ The BMI was used as a proxy for adiposity for all analytic procedures to better quantify associations between cortical thickness brain regions and more severe levels of obesity that would be obscured with the use of BMI z scores or BMI percentiles for age and sex.⁴² Cortical thickness was the primary response variable, and BMI was the primary explanatory variable of interest. Additional covariates included in the GLM were intracranial volume (ICV), age, sex, handedness, MRI scanner serial number, puberty, and race. The 2-tailed α was set at .05. The Bonferroni method was used to adjust for multiple comparisons.

Associations Between BMI and Whole Cortex

To complement our analysis that explored associations between the thickness of individual cortical regions and BMI, models to predict the converse association (ie, to predict BMI based on the thickness of all cortical regions with and without demographic measures) were created using elastic net regularized regression.⁴³ The initial variable set included 66 cortical measures and 7 additional covariates (ie, age, ICV, puberty, handedness, race, age, MRI scanner, and sex). This allowed us to explore how much variance in BMI was associated with the potential contribution of all cortical regions. Elastic net regularization provides a robust, parsimonious model to explain associations between variables of interest that are highly collinear by using both L_1 and L_2 penalties to combine feature selection with inclusion of correlated features.⁴⁴ To prevent bias and overfitting associated with the large number of variables in our prediction model approach, we used 10-fold nested cross-validation (giving a total of 100 model fits) to enable tuning of the 2 regularization parameters (ie, L_1 and L_2).⁴⁵ In any single fold, the training set was composed of 90% of the individuals with testing performed on the remaining 10% of individuals. In addition, the entire fitting was repeated 5 times to estimate uncertainty in the resulting scores and further improve the models' predictive power. The elastic net fitting and nested cross-validation were implemented using Scikit-Learn, version 0.19 in Python software, version 3.7 (Python Software Foundation).⁴⁶ The quality of each model fit was reported as the Pearson correlation between the fit estimates (ie, testing model) and the true BMI (ie, training model) and as the percentage of variance in BMI explained by the model. The performance of the model was evaluated by how well it performed on aspects of the data not included in the initial model construction, thereby quantifying the generalizability and reproducibility of the results. The 2-tailed α was set at .05.

Association Between BMI and Executive Function

Pearson partial correlations were computed to investigate any significant associations between BMI and the 4 cognitive measures of interest while controlling for age, sex, race, ICV, handedness, and puberty. Cognitive measures that were signifi-

cantly associated with BMI were used for mediation analysis to further explain the association among BMI, executive function, and cortex. Data were analyzed using SPSS software, version 23⁴⁷ with a 2-tailed $\alpha = .05$.

Prefrontal Cortex, BMI, and Executive Function Mediation Analysis

Because the results of the initial GLM revealed that the strongest association between BMI and cortical thickness was in the prefrontal cortex, a mediation analysis was performed to assess whether mean prefrontal cortical thickness mediated the association between BMI and executive function. The mean thickness of all cortical regions located within the prefrontal cortex was calculated. Only individuals who had structural imaging and complete cognitive data were included. Mediation models were tested using PROCESS, a macro developed for SPSS software, version 23 (SPSS Inc)⁴⁷ by Andrew Hayes (<http://processmacro.org/>). PROCESS uses observed variable ordinary least squares path analysis to estimate direct and indirect effects.^{48,49} Significance of indirect effects of the mean prefrontal cortical thickness was assessed by 1000 bootstrap 95% CIs. Simulation research indicates that the bootstrap method is more robust to nonnormality and has better type I error control than the causal steps method and the Sobel test.⁴⁹ Covariates used in the models included age, sex, ICV, race, puberty, handedness, and MRI scanner. All paths are reported as unstandardized ordinary least squares regression coefficients. Concretely, the analyses were based on model 4 in the macro. The BMI was modeled as the associated variable, mean prefrontal cortical thickness was included as the mediating variable, and each of the cognitive measures were assessed separately as the outcome variable. That is, 4 models were tested corresponding to each of the 4 cognitive measures. Each cognitive measure was tested because multiple factors may contribute to cortical thickness, some in opposing directions. Unknown or unaccounted factors that have not been expressly included in the mediation model could have obscured the apparent association between BMI and cognitive function.

Results

Of the 4524 individuals in the ABCD study curated release 1.0, 4329 had complete imaging data. Imaging data from 767 individuals were excluded because of excessive head motion and/or failure to pass acceptable study quality control measures. Therefore, 3190 individuals (mean [SD] age, 10.0 [0.61] years; 1627 [51.0%] male) had complete demographic data and were included in the analysis. The demographics of the study participants are presented in **Table 1**.

Regional Associations Between BMI and Cortical Thickness

Overall, higher BMI was associated with lower cortical thickness (eTable 1 in the **Supplement**). **Figure 1** provides a *t* statistic brain map that shows the overall change in cortical thickness associated with BMI without statistical thresholding. eTable 2 in the **Supplement** gives the mean cortical thickness for each cortex region. Eighteen cortical regions were significantly and inversely associated with BMI after

Table 1. Sample Characteristics^a

| Characteristic | Aggregate (n = 3190) | Subsample (n = 2418) |
|----------------------------|----------------------|----------------------|
| Age, mean (SD), mo | 120.2 (7.3) | 120.1 (7.2) |
| Race | | |
| White | 2663 (84) | 2026 (83.8) |
| Black | 435 (13.6) | 321 (13.3) |
| Asian | 179 (5.6) | 127 (5.3) |
| Female | 1563 (49.0) | 1166 (48.2) |
| BMI ^b | | |
| Mean (SD) | 18.64 (3.9) | 18.65 (3.9) |
| 85% to <95% | 429 (13.4) | 322 (13.2) |
| ≥95% | 491 (15.4) | 357 (14.8) |
| Pubertal stage by sex | | |
| Before | | |
| Female | 511 (16.0) | 388 (16.0) |
| Male | 1166 (36.6) | 907 (37.5) |
| Early | | |
| Female | 373 (11.7) | 297 (12.3) |
| Male | 375 (11.8) | 284 (11.7) |
| Mid | | |
| Female | 604 (18.9) | 427 (17.7) |
| Male | 62 (1.9) | 44 (1.8) |
| Late | | |
| Female | 37 (1.2) | 28 (1.2) |
| Male | 6 (0.2) | 4 (0.2) |
| After | | |
| Female | 0 | 0 |
| Male | 0 | 0 |
| Right-handed | 2532 (79.4) | 1926 (79.7) |
| Total parent income, \$ | | |
| ≤25 000 | 508 (15.9) | 356 (14.7) |
| >25 000 to <50 000 | 714 (22.4) | 556 (23.0) |
| >50 000 to <75 000 | 517 (16.2) | 400 (16.6) |
| >75 000 to <100 000 | 1046 (32.8) | 799 (33.0) |
| ≥200 000 | 405 (12.7) | 307 (12.7) |
| Highest parental education | | |
| Less than high school | 95 (3.0) | 65 (2.7) |
| High school | 282 (8.9) | 293 (8.0) |
| Some college | 502 (15.7) | 387 (16.0) |
| Associate's degree | 380 (11.9) | 301 (12.4) |
| Bachelor's degree | 1011 (31.7) | 764 (31.6) |
| Master's degree | 708 (22.2) | 539 (22.3) |
| Doctoral level | 212 (6.6) | 169 (7.0) |

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

^a Data are presented as number (percentage) of patients unless otherwise indicated.

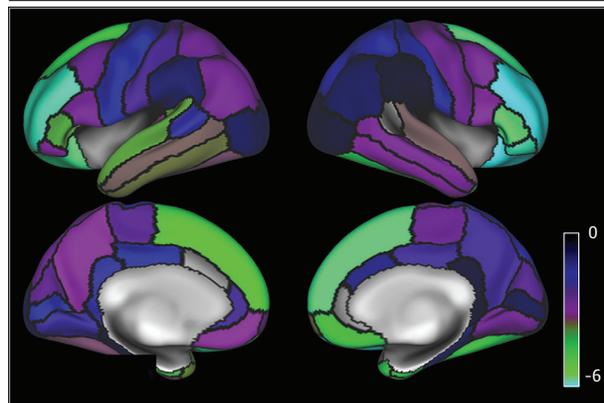
^b BMI according to Centers for Disease Control and Prevention criteria: 85th to 95th percentile for age and sex is considered overweight; 95th percentile and greater is considered obese.

adjustment for multiple comparisons (**Table 2**). The strongest associations were observed in the prefrontal cortex.

Associations Between BMI and Whole Brain Cortex

The 10-fold nested cross-validation model using only demographic data (ie, no cortex) indicated a mean *r* of 0.359

Figure 1. t Statistic Map Demonstrating the Associations Between Regional Parcellations of Cortical Thickness and Body Mass Index (BMI)



Brain map parcellation according to the Desikan-Killiany atlas. Regions are outlined in black. Cyan brain regions (t statistic, -6) demonstrate the strongest association between higher BMI and thinner brain cortical region. Indigo regions demonstrate weaker associations ($t = -3.5$) between BMI and brain cortical region.

between the fit estimates (ie, testing model) and the BMI (ie, training model) and explained a mean (SD) of 12.9% (0.1%) of the variance between BMI and demographics (eg, sex, race, and age). The model allowing demographic data and all cortical regions indicated a mean r of 0.388, with a mean (SD) of 14.94% (0.1%) of the variance among BMI, demographics, and cortical thickness.

BMI and Neurocognitive Partial Correlates

Of the 3190 individuals, 772 lacked complete data for the full cognitive task battery, further restricting the sample size to 2418 (75.8%). The BMI was significantly and inversely correlated with dimensional card sorting ($r = -0.088$, $P < .001$), list sorting ($r = -0.061$, $P < .003$), and matrix reasoning ($r = -0.095$, $P < .001$) but not the flanker task. eTable 3 in the Supplement details the descriptive statistics of neurocognitive scores for each task.

Mediation Analysis of Prefrontal Cortex, BMI, and Executive Functioning

Mediation analysis was used to test the hypothesis that BMI is associated with alterations in prefrontal cortical thickness and diminished cognitive function. The reported coefficients are unstandardized. After partialing out the influence of the covariates, BMI was significantly associated with list sorting alone and when mean prefrontal cortical thickness was included as a mediator (Figure 2). In the PROCESS analysis toolbox, a significant indirect effect is indicated when the bootstrap CI does not include zero. There was a significant positive indirect effect of BMI associated with list sorting through prefrontal cortical thickness (mean [SE] indirect effect, 0.014 [0.008]; 95% CI, 0.001-0.031). No significant indirect effects of prefrontal cortical thickness were found for the matrix reasoning (mean [SE] indirect effect, 0.001 [0.002]; 95% CI, -0.002 to 0.004), dimensional card sorting (mean [SE] indirect effect, 0.008 [0.081]; 95% CI, -0.008 to 0.025), or the flanker task (mean [SE] indirect

Table 2. Cortical Brain Regions Demonstrating an Association With Body Mass Index

| Cortical Region | t Statistic ^a |
|------------------------------|--------------------------|
| Left cortical hemisphere | |
| Rostral middle frontal gyrus | -5.77 |
| Lateral orbitofrontal | -5.58 |
| Superior frontal gyrus | -4.86 |
| Entorhinal | -4.19 |
| Pars triangularis | -3.96 |
| Superior temporal lobe | -3.87 |
| Temporal pole | -3.74 |
| Inferior temporal lobe | -3.58 |
| Right cortical hemisphere | |
| Rostral middle frontal gyrus | -7.55 |
| Lateral orbitofrontal | -5.95 |
| Pars orbitalis | -5.75 |
| Superior frontal gyrus | -5.58 |
| Pars triangularis | -5.55 |
| Temporal pole | -4.61 |
| Fusiform gyrus | -4.53 |
| Entorhinal | -4.49 |
| Medial orbitofrontal | -4.45 |
| Frontal pole | -3.6 |

^a Significant with a Bonferroni threshold of $P < .001$ for all.

effect, 0.002 [0.008]; 95% CI, -0.012 to 0.018) (eFigure in the Supplement).

Discussion

Higher BMI was associated with thinner cortex in widespread parts of the brain in a large sample of 3190 children aged 9 and 10 years. These associations were significant in 18 of the 66 cortical regions examined individually. In all but 3 of the remaining 45 regions, the thinner cortical thickness was associated with higher BMI (eTable 1 in the Supplement), although these associations did not individually pass the threshold of significance for an exploratory analysis.

The strongest of the BMI associations were observed in the prefrontal cortex (Figure 1), which represents mental processes critical to decision-making and the planning of complex behavior.^{9,10} Greater BMI was significantly associated with poorer performance on several executive functions, including list sorting,⁵⁰ card sorting,^{51,52} and matrix reasoning,⁵¹ which are known to depend on the integrity of the prefrontal cortex. Further analysis indicated that the association between BMI and list sorting, an index of working memory, was partially mediated by mean prefrontal cortex thickness. This finding is consistent with the hypothesis that BMI affects cortical development in a way that is detrimental to cognitive function.

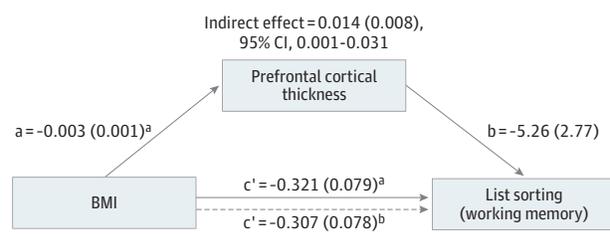
Several other studies^{12,50} have observed a similar association between BMI and executive function, generating speculation that dysregulation of these cognitive functions could exacerbate poor decision-making with regard to diet and thus

contribute to negative health outcomes, including excessive weight gain. Goldschmidt et al,⁵³ using a similar cognitive battery, reported that children who were overweight with and without loss of control eating had deficits in working memory compared with lean children. Riggs et al⁵⁴ found that alterations in working memory appeared to be antecedent to weight gain, with such deficits being associated with increased risk of becoming overweight among children.⁵⁵ The present study advances our working hypothesis by identifying a plausible brain mechanism underlying this association. Additional prospective studies will be required to determine how lower cognitive functioning in these domains might contribute to higher BMI, either as a direct influence on dietary choices or perhaps an indirect influence related to higher general stress resulting from diminished ability to succeed at age-specific challenges relative to peers.

The current findings are based on a larger sample than any previous study, to our knowledge. Several of these studies^{15,56,57} did not find associations between otherwise healthy children with obesity and cortical abnormalities. However, brain alterations have been found in obese youth with metabolic syndrome, insulin resistance, and/or type 2 diabetes.⁵⁸ Lower gray matter volume predominantly in the orbitofrontal cortex and anterior cingulate as well as lower hippocampal volumes have been reported in obese adolescents with metabolic syndrome. Obese children with early-onset type 2 diabetes were reported to have lower white matter tract integrity⁵⁹ and prefrontal volume and global cerebral atrophy.⁶⁰ In the present study, the right and left medial and orbitofrontal cortex areas were among the cortical areas most strongly associated with BMI (*t* statistic, ≥ 3.54 to -5.92) (Figure 1). The orbitofrontal cortex has been associated with salience attribution, hedonic valuation, and food choice.⁶¹⁻⁶³ Thus, maladaptive valuation processes may also contribute to poor dietary decision-making. In addition, the explanatory contribution of cortical thickness to BMI is not large. In the current analyses, when demographic factors and all brain regions were included in a single model predicting BMI, only an additional 2% of the variance was explained beyond a simple model that included demographic factors alone.

A medical history of metabolic syndrome, insulin resistance, and/or metabolic markers (ie, insulin levels, C-reactive protein, and lipid analysis) was not obtained in this sample. As a consequence, it is not possible to determine the extent to which lower cortical thickness and poorer working memory in this sample are attributable to the unknown presence of metabolic syndrome and/or insulin resistance.^{12,64} Many pathophysiologic manifestations of obesity could produce brain abnormalities during development. Escalating levels and persistence of adiposity are associated with subclinical oxidative stress, inflammation, metabolic dysfunction, and vascular reactivity that may disrupt cellular development, vessel integrity, and neuronal architecture within the brain early in childhood. Excessive circulating inflammatory biomarkers, such as interleukin 1 β , interleukin 6, and C-reactive protein, have been associated with increasing white adipose tissue and BMI. Intimal thickening, vascular stiffness, and fatty streaking have been re-

Figure 2. Mediation Model Demonstrating Associations Among Body Mass Index (BMI), Prefrontal Cortex, and Working Memory



Dotted line indicates the association of BMI with working memory when the mediating variable (prefrontal cortex) is included in the model. All paths are reported as unstandardized ordinary least squares regression coefficients.

^a $P < .05$.

^b $P < .001$.

ported in otherwise healthy children who were obese, both of which may be associated with altered cerebral blood flow and changes in neuronal activity.^{65,66} Microstructural changes in dendritic spine density, synaptic proteins, and microglial alterations in the prefrontal cortex have been found in rodent models after diet-induced obesity (ie, weight gain of 25% of body weight) in as early as 8 weeks, suggesting that the transition from lean to obesity may cause cellular changes within the brain.⁶⁷ The prefrontal cortex may be more vulnerable to the negative effects of obesity because of its later maturity compared with other brain regions during adolescence, accounting for the particularly robust association of BMI with the prefrontal cortex in the present study.^{68,69}

Limitations

Several factors limit the interpretation of the current findings. Metabolic information was not collected for participants. Body mass index is an indirect measure of adiposity, and as such, the use of BMI as a marker for metabolic derangement and the lack of metabolic information limits inferences and requires further investigation. However, BMI is strongly associated with total body adiposity in otherwise healthy pediatric populations.^{70,71} An alternate association for the present findings cannot be ruled out. It is possible that thinner cortex interferes with working memory in a way that is associated with higher BMI. The cross-sectional nature of the first ABCD study data release does not permit inferences about whether cortical thickness decreased as a result of higher BMI or whether lower cortical thickness facilitated higher BMI.⁵⁴ In addition, the automated estimation of cortical thickness may conflate absolute thickness with changes in the distinctness of the boundary between the cortex and the underlying white matter during development. Mean prefrontal cortical thickness might not be sensitive enough to capture neurocognitive changes that were mediated by specific brain areas within the whole frontal lobe. The exploratory nature of the current study will refine this question for future time points in the ABCD study data set. In addition, cortical parcellation of the insula was not available and thus not included in the present analysis. Consequently, the current study does not provide negative evidence about the interaction of BMI with gray matter volume in the insula.

Conclusions

In this study, greater BMI was associated with lower cortical thickness in children. This association was strongest in the prefrontal cortex. Furthermore, prefrontal cortex thickness appeared to mediate the association between BMI and working memory. Although it is not possible to determine from a cross-sectional sample the causal relationship among BMI, cortical thickness, and cognitive ability, these findings sug-

gest that BMI is associated with alterations in prefrontal cortex development and diminished executive function, such as working memory. Deficits in working memory may in turn contribute to poor dietary decision-making. Once established, these associations may become mutually reinforcing and contribute to ongoing health issues that persist into adulthood. Autoregressive modeling of future data releases from the longitudinal ABCD study will clarify the potential causal interactions among BMI, brain structure, and executive function over time.

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Drafting of the manuscript: Laurent, Mackey.

Critical revision of the manuscript for important intellectual content: All authors.

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