JCI insight

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JCI Insight. 2024. https://doi.org/10.1172/jci.insight.181690.

Clinical Medicine In-Press Preview Development Neuroscience

Childhood obesity and its adverse health consequences have risen worldwide, with low socioeconomic status increasing the risk in high-income countries like the US. Understanding the interplay between childhood obesity, cognition, socioeconomic factors, and the brain is crucial for prevention and treatment. Using data from the ABCD study, we investigated how body mass index (BMI) relates to brain structural and functional connectivity metrics. Obese/overweight children (n = 2,356) were more likely to live in poverty and exhibited lower cognitive performance compared to normal weight children (n = 4,754). Higher BMI was associated with multiple brain measures that were strongest for lower longitudinal diffusivity in corpus callosum, increased activity in cerebellum, insula, and somatomotor cortex, and decreased functional connectivity in multimodal brain areas, with effects more pronounced among children from low-income families. Notably, nearly 80% of the association of low income and 70% of the association of impaired cognition on BMI were mediated by higher brain activity in somatomotor areas. Increased resting activity in somatomotor areas and decreased structural and functional connectivity likely contribute to the higher risk of overweight/obesity among children from low-income families. Supporting low-income families and implementing educational interventions […]

Childhood Obesity's Impact on Cognition and Brain Connectivity Worsens with Low Family Income

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Abstract

Childhood obesity and its adverse health consequences have risen worldwide, with low socioeconomic status increasing the risk in high-income countries like the US. Understanding the interplay between childhood obesity, cognition, socioeconomic factors, and the brain is crucial for prevention and treatment. Using data from the ABCD study, we investigated how body mass index (BMI) relates to brain structural and functional connectivity metrics. Obese/overweight children (n=2,356) were more likely to live in poverty and exhibited lower cognitive performance compared to normal weight children (n=4,754). Higher BMI was associated with multiple brain measures that were strongest for lower longitudinal diffusivity in corpus callosum, increased activity in cerebellum, insula, and somatomotor cortex, and decreased functional connectivity in multimodal brain areas, with effects more pronounced among children from low-income families. Notably, nearly 80% of the association of low income and 70% of the association of impaired cognition on BMI were mediated by higher brain activity in somatomotor areas. Increased resting activity in somatomotor areas and decreased structural and functional connectivity likely contribute to the higher risk of overweight/obesity among children from low-income families. Supporting low-income families and implementing educational interventions to improve cognition may promote healthy brain function and reduce the risk of obesity.

Introduction

Pediatric obesity has been on the rise worldwide, and current estimates indicate that 19.7% of children are obese in the US (1). Several factors contribute to pediatric obesity, including low family income (2), genetics (3), environmental factors such as food desserts, lack of open spaces for exercising, among others (4). Because childhood obesity can interfere with normal brain development (5-8) and has been associated with diminished cognitive function (7, 9, 10), it is urgent to understand better how it influences brain function.

The brain matures rapidly in early childhood, achieving approximately 90% of its adult size by age 6. Additionally, as children progress through late childhood and adolescence, white matter (WM) volume and the fractional anisotropy (FA) of the WM fiber bundles generally increase, whereas gray matter volume decreases and brain functional connectivity reorganizes, decreasing in some networks while increasing in others (11-13). While the relationship between BMI and brain structural and functional connectivity is complex and potentially bidirectional, the exact mechanisms and the extent to which body mass index (BMI) is associated with alterations in structural and functional connectivity during brain development remain poorly understood. Furthermore, because poverty also negatively impacts brain development and cognitive function (14-18), it is also relevant to assess the impact of family income on the relationship between BMI and brain connectivity and cognition. A better understanding of the complex interplay between BMI and brain development could help guide prevention and treatment strategies for childhood obesity (19).

Here we measured the associations between BMI and brain activity, connectivity (structural and functional), and cognitive performance and assessed the influence of family income on these associations. We hypothesized a bidirectional association between BMI and brain structure, function, and cognitive performance, which may be exacerbated among children from low-income families. For this purpose, we

used the baseline data from the Adolescent Brain Cognitive Development (ABCD) study, which was collected when children were 9–10-years-old and divided the sample into Discovery and Replication subsamples, to assess the reproducibility of the findings.

To measure the structural connectivity provided by white matter fibers, we used diffusion Tensor Imaging (DTI) metrics, including FA, mean (MD), longitudinal or axial (lD), and radial (rD) diffusivity (8). To measure resting brain activity we mapped the fractional amplitude of low-frequency fluctuations (fALFF), which measures spontaneous brain activity (20). To quantify resting functional connectivity we mapped global functional connectivity density (gFCD) (21), a measure that is sensitive to both cognitive performance (22) and family income (15). To assess cognition we used the composite scores of crystallized, fluid, and total intelligence (23). Given the associations of BMI with WM integrity previously observed in children (8, 14), we specifically hypothesized that higher BMI would be associated with lower cognitive performance, higher resting brain activity in primary cortical areas, and weaker structural and functional connectivity, and that these effects would be exacerbated in children from low-income families. To address the complexity of these relationships, we employed Causal Mediation Analysis (CMA) to examine the hypothesized bidirectional associations. In our models, we treated BMI as both an independent and dependent variable, enabling us to test the directionality of its effects on brain and cognitive outcomes. We included family income as a moderator to explore how socioeconomic status influences these relationships.

Results

Demographic characteristics

Among the 7110 children in the present study, 4754 were normal weight (67%) and 2356 overweight or obese (33%) based on the 85th percentile for BMI according to age and sex. This classification method is standard in pediatric studies, as it accounts for the variations in BMI that occur

naturally with growth and development (24). Therefore, overweight and obesity in children are not defined using a fixed BMI threshold (such as BMI > 30, which is used for adults). These proportions align with the reported rate of overweight or obese (35.4%) among American children and adolescents aged 2-19 years in the 2017-2018 period (25), which corresponds to the time frame when the ABCD baseline data was collected. Analysis of racial and ethnic differences revealed a higher percentage of obese and overweight children from African American (30% and 18%) and Hispanic (25% and 19%) families compared to White families (10% and 14%). Analyses of income differences revealed that obese and overweight children were more likely to reside in poverty (defined in the US as a family income below $25,000) than normal weight children, with odds ratios of .20 and .15 for obese and overweight children, respectively, compared to .09 for normal weight children. Obese/overweight children were more likely to show depression symptoms than normal weight children (6.1% vs 3.3%; $\chi^2(1, N=4,422) = 16.4$, P=3.3E-05).

Discovery and Replication subsamples

The proportions of normal and obese/overweight children did not differ between the Discovery and Replication samples (χ^2=2.3; P=.13). There were minimal differences in brain volume, sex, and the proportion of MRI manufacturers between the Discovery and Replication subsamples (Table 1).

Reproducibility of BMI, demographics, and cognition by weight category

BMI displayed consistent right-skewed distributions (skewness=1.5, kurtosis=4.0) in both the Discovery and Replication datasets, which were explained by the weight categories (Figure 1A). There were no differences in BMI between genders (Supplemental Figure S1). Normal weight and obese/overweight children showed similar increases in BMI with age (Figure 1B). BMI showed a negative correlation with family income bracket, such that higher BMI was associated to lower family income,

which was significant independently in the obese/overweight and the normal weight groups both for the Discovery and Replication samples Figure 1, C and D). However, note that in the normal weight group the correlations for the discovery (r= -.094) and replication (r=-.077) samples were very small (Figure 1, C and D).

Cognitive scores differed between groups being lower for obese/overweight than for normal weight children both for the Discovery and Replication samples (Figure 1F). Among obese/overweight children, BMI was negatively correlated with total cognitive composite scores, such that higher BMI was associated with lower scores, whereas the correlation was not significant among normal weight children (Figure 1E) suggesting a threshold effect at which BMI negatively impacts cognition. The main effects on BMI of weight category, family income bracket, and total cognitive composite, and the interaction between weight category and family income was significant, independently in Discovery and Replication subsamples ($P<7E-5$; $F(1,3240)>15.8$; ANCOVA; Supplementary Table S1).

Associations of Age, BMI and Family Income with Structural connectivity

We used ANCOVA to investigate the associations of age and BMI on WM integrity. The model included 2 weight categories/groups (overweight/obese and normal weight), 2 independent variables (age and BMI), and a dependent variable (FA, MD, lD, or rD). Independent ANCOVAs were conducted for each DTI metric and ROI. Our analysis revealed negative associations of MD with age and lD with BMI and positive association of age with FA (Figure 2, A and B). Though older age was linked to higher FA and lower MD, lD, and rD (Figure 2, A and C), age-related changes were more notorious for MD than for FA, lD, and rD, particularly in superior cortico-striatal fibers.

Elevated BMI was linked to reduced age-corrected lD across many fiber bundles, notably pronounced in the corpus callosum ($R(4,796)=-.24$; $p<2E-16$; Cohen's $d=.49$; Figure 2B), forceps minor, uncinate, anterior thalamic radiations, parahippocampal-cingulum and cingulate-cingulum fiber bundles

(R(4,796)<-.15; p<2E-16). The negative correlations in parietal and frontal cortico-striatal bundles were not consistently reproducible. Higher BMI was consistently associated with decreased age-corrected MD and rD bilaterally in various regions, including the uncinate and striatal inferior frontal, cingulum-cingulum fiber bundles, corpus callosum, forceps minor and major, as well as left fornix, the superior cortico-striatal frontal fiber bundle, and left anterior thalamic radiations (see Figure 2B). Additionally, increased BMI was linked to decreased age-corrected FA in several regions, including bilateral fornix, right superior longitudinal fasciculus, as well as in right inferior to superior frontal, longitudinal fasciculus to right temporal cortex, and bilateral superior parietal cortices white matter fiber bundles.

Separate analyses by weight groups showed that lD in corpus callosum decreased with age in both groups, (Figure 2C) and was lower in obese/overweight than in normal weight children (Figure 2D). lD in corpus callosum had reproducible positive associations with family income in both obese/overweight and normal weight children, and with fluid composite scores in obese children (R(404)>.11; P<.045, 2-sided), but the association in normal weight children was not reproducible (Figure 2, D-F). The negative correlation between BMI and lD in corpus callosum was significantly stronger for obese/overweight than for normal weight children, independently for the Discovery and Replication samples (z>4, P<1E-05; Figure 2D). The main effects of age, BMI, weight category, total cognitive composite, and family income on lD in corpus callosum were significant (F(1,4410)>9, P<.003; ANCOVA; Table S2).

Association of BMI with brain activity and functional connectivity

To assess BMI-related differences in resting brain activity and functional connectivity across children we used fALFF and gFCD, metrics, which showed high reproducibility in Discovery and Replication subsamples (Supplemental Figures S2 and S3). Vertex-wise ANCOVA revealed a positive association between BMI and fALFF, which was maximal in cerebellum (Cohen's d=.12) and significant bilaterally in all subcortical regions (Supplemental Figure S4), insular-opercular, somatomotor, and premotor areas,

paracentral lobe, orbitofrontal cortex, mid cingulum, early and MT+ visual areas, and lateral and medial temporal cortices (P_{FDR}<.05; Figure 3A). This pattern exhibited a high level of reproducibility in the Discovery and Replication subsamples (Supplemental Figure S5). The overlap of the BMI-fALFF correlation pattern in the dorsolateral prefrontal, superior and inferior parietal cortices (including the precuneus) was minimal (~6%; Supplemental Figure S6), suggesting a weak association between BMI and fALFF in these regions. In contrast, higher BMI was associated with lower gFCD, which was maximal in the precuneus (area 7m; Cohen's d=.18) and also significant bilaterally in other default-mode network (DMN) regions (posterior cingulum, angular gyrus, and medial prefrontal cortex, PFC), in superior frontal, inferior and middle temporal gyri, primary and secondary visual areas, inferior and superior parietal cortices, premotor cortex, dorsolateral PFC, frontal pole, and the anterior cerebellar lobe (P_{FDR}<.05; Figure 3B). These patterns had high reproducibility in the Discovery and Replication subsamples (Supplemental Figure S7).

We applied a functional specialization index (26) that distinguishes between unimodal cortical regions (such as visual, auditory, and somatomotor cortices), characterized by a high specialization index (>.5), from heteromodal association cortical areas (such as the insula, dorsolateral prefrontal cortex, and inferior parietal cortex), characterized by a lower specialization index, to map the associations with BMI. The BMI associations with fALFF had a more pronounced overlap with unimodal areas (36%) than the BMI associations with gFCD (11%) (Figure 3).

Associations of fALFF and gFCD, with cognition, family income, and FA

To examine the associations between BMI, resting-state metrics (fALFF and gFCD), and cognitive composite scores as a function of family income we measured their Pearson correlations within specific ROIs of a multi-modal parcellation of the human cerebral cortex (27) across weight categories. Lower cognitive performance correlated with higher fALFF, predominantly in insula, cingulate and somatomotor cortices, and subcortical and cerebellar regions (Figure 4A). This association was consistent across normal

weight and obese/overweight children in both Discovery and Replication subsamples (Supplemental Figures S8 and S9; R>.14, P<2E-08). Moreover, lower family income was linked to higher fALFF in occipital and medial temporal areas, insula, mid cingulum, and the somatomotor cortex (Figure 4B), independently across weight categories and subsamples in the Discovery and Replication subsamples (Supplemental Figures S8 and S9; R>.09, P<.001). Additionally, lower cognitive performance was associated with lower gFCD in DMN and frontoparietal network (FPN) regions alongside higher gFCD in lateral visual areas, the paracentral lobe and mid cingulate cortex (Figure 4A); this relationship was consistent across weight categories and subsamples (Supplemental Figures S9 and S20; R>.74, P<.003). Furthermore, lower family income was correlated with lower gFCD in FPN and DMN regions and with higher gFCD in lateral visual areas, somatomotor cortex, paracentral lobe, and mid cingulate cortex (Supplemental Figures S9 and S10; R>.072, P<.007). The correlation patterns for fALFF and gFCD were largely complementary of one another, both in Discovery and Replication subsamples, such that brain regions with high correlation for fALFF had low correlation for gFCD (family income: R(379)>.64; total composite: R(379)>.52; P<1E-20). While the correlations reported are significant (ranging from approximately .06 to .15) and reproducible, they exhibit modest effect sizes, which were detectable due to the large sample size of the ABCD study.

Higher average FA throughout the brain's white matter tracts was associated with elevated gFCD and lower fALFF, independently across weight categories (R>.14; P<1.5E-08; Figure 4A).

Effect of BMI within subcortical regions and cerebellum

We also evaluated associations between BMI, resting-state activity, and connectivity within subcortical ROIs. The positive associations of BMI with fALFF were reproducible bilaterally, in all 19 subcortical ROIs (P<.05, Bonferroni-corrected) and did not differ between weight categories (Supplemental Figure S11); those with gFCD were reproducible only in the bilateral cerebellum. Within the cerebellum there were reproducible positive associations with BMI for fALFF, bilaterally in lobules IV,

V, VIIIb, and IX which did not differ between weight categories. The slopes of the linear associations of BMI with gFCD were negative, bilaterally in lobules IV, VI, VIIb, VIIIa, and IX, and Crus I (excluding vermis) and Crus II, V (right), and VIIIb (vermis), and those in bilateral posterior cerebellum (lobules VIIb and VIIIa, and vermis VIIIa) were weaker for obese/overweight than normal weight children (P<.001, two-sided t-test).

Causal mediation analysis (CMA)

We used CMA model 1 to investigate the indirect pathways linking family income and cognitive performance to BMI through fALFF or gFCD (Figure 5, A and D). Our analysis revealed consistent indirect associations of family income on BMI, mediated through fALFF in bilateral somatomotor areas, insula, cingulum, and cerebellum, as well as through gFCD bilaterally in FPN and DMN regions (P_{ACME}<.001; Figure 5, B and C, Supplemental Figures S12 and S13). Specifically, the bilateral superior frontal language (SFL) and visual cortex (V3) and premotor (6d) areas demonstrated the strongest mediation effects of fALFF on the association between family income and BMI (>78%; Supplemental Figure S13). For family income, the average mediation proportion was higher for fALFF (Discovery: 37%, Replication: 36%) than for gFCD (Discovery: 14%, Replication: 7%; t(436)>10; P<2E-21). Moreover, both fALFF and gFCD in these regions consistently acted as partial mediators for the association between cognitive performance and BMI (P_{ACME}<.001; Figure 5, E and F, and Supplemental Figure S14). For total composite scores, the average mediation proportion was also higher for fALFF (Discovery: 31%, Replication: 32%) than for gFCD (Discovery: 7%, Replication: 11%; t(624)>14; P<4E-42). The regions where fALFF mediated the indirect effects of total cognition on the BMI association were more widespread than those observed for mediating the indirect effects of family income on BMI.

Additionally, we utilized CMA model 2 to complement our analysis by examining the indirect pathways linking the association of brain functional connectivity to BMI through family income and

through cognitive performance (Supplemental Figure S15). Our analysis revealed weak yet consistent mediation effects of family income on the associations between BMI and fALFF in bilateral insula and mid cingulum (Supplemental Figure S15), and between BMI and gFCD bilaterally in FPN and DMN regions (P_{ACME}<.001; Supplemental Figure S16). For family income, the average mediation proportion was higher for gFCD (Discovery: 5%, Replication: 4%) than for fALFF (Discovery: 2%, Replication: 2%; t(243)>6.8; P<1E-10). Additionally, cognitive performance consistently acted as a modest mediator between fALFF or gFCD in these regions and BMI (P_{ACME}<.001; Supplemental Figures S15 and S16). Specifically, for total composite scores, the average mediation proportion was higher for gFCD (Discovery: 9%, Replication: 9%) than for fALFF (Discovery: 7%, Replication: 6%; t(293)>3.9; P<1E-04). The proportion of mediation from CMA model 1 was greater than that from CMA model 2.

Discussion

The high prevalence of obesity in American children has raised concerns about its implication to brain development, as evidence is emerging that obesity in children is linked to adverse effects on brain function and structure and on cognition (5-10). Access to the large longitudinal data set from the ABCD have increased the power to investigate the effects of obesity on brain structure (including white matter integrity), function (including functional connectivity), and cognition (28, 29). However, the reproducibility and implications of these effects (30) remain unclear. Here we investigated the effects of BMI on DTI and resting-state fMRI metrics using the large cohort of US children from the ABCD study while strictly controlling for confounding demographic variables (e.g., age, sex, race), head motion, and brain volume, and for study-specific variables (scanner manufacturer and research site) separately in Discovery and Replication samples. We found that BMI was associated positively with spontaneous brain activity, as indexed by fALFF, and negatively with brain connectivity (structural and functional), family income, and with cognition, reproducibly in the Discovery and Replications subsamples. The spontaneous brain activity (predominantly in somatomotor areas) partially mediated the outcomes, such that close to 80% of the total effects of family income and cognitive performance on their association with BMI were mediated by fALFF in the somatomotor cortex. This suggests that changes in socioeconomic status or in cognitive performance may influence BMI partly through their impact on brain activity in these brain regions. Notably, the mediation effects of fALFF on the association between cognitive performance and BMI were more widespread in the brain than those observed for family income, indicating that cognition contributes to BMI independently of family income.

We found a reproducible association between elevated BMI and reduced lD in the corpus callosum (Cohen's d=.49), along with a less pronounced yet still significant association with other WM tracts. Axial diffusivity (lD) measures the rate of diffusion of water molecules along the primary axis of

WM fibers and provides information about WM microstructural integrity (31). The corpus callosum plays a crucial role in functional lateralization and in the coordination of cognitive, sensory and motor systems that are needed for conscious experience (32). Our findings are consistent with those of prior DTI studies in adults and adolescents that reported correlations between BMI and decreased FA or increased MD in the corpus callosum (28, 33-41), and with the notion that WM integrity is compromised in obesity (29) (see review by Kullmann et al (8)). The lower longitudinal water diffusion in this region may indicate reduced interhemispheric connectivity, which could reduce the integration of information between left and right cortical areas and contribute to the cognitive impairment reported in children with high BMI (42, 43). The reproducible linear associations of FA with fALFF and gFCD are consistent with the assumption that brain activity and functional connectivity are influenced by the structural connectivity of the brain (44).

Higher BMI was associated with increased fALFF in interoceptive, somatomotor, medial visual, subcortical, and cerebellar regions (Cohen's d=.11). This suggests increased local neuronal activity in these regions in obese and overweight, compared to normal weight children. These findings are consistent with reports of higher synchrony or amplitude of spontaneous resting activity in the brain for obese compared to lean men (45, 46).

In contrast to the positive association between BMI and fALFF, the association with gFCD was negative and predominantly impacted multimodal association cortices. Children with high BMI displayed lower gFCD, with the strongest effects in default-mode and cingulo-opercular regions (Cohen's d=.16). gFCD maps the overall functional integration of brain regions (21), contrasting the few metabolically demanding hubs (47) that orchestrate major resting state networks (48) with the abundant weakly interconnected brain network nodes (49). The strongest association with gFCD was in the precuneus, which is one of the main hubs in the brain (49) that engages in highly integrated internally and externally driven processes (50). The opposite pattern between fALFF and gFCD with BMI is reminiscent of a pattern

we previously reported for the effects of methylphenidate (51). Though methylphenidate is prescribed to improve attention in ADHD children (52), it also leads to weight loss and has been used to reduce weight in obese children (53). Inasmuch as increased gFCD in precuneus was associated with higher cognitive scores in the current study, it suggests that reduced gFCD might contribute to processes that increase risk for obesity and impair cognitive performance.

Our findings were reproducible in Discovery and Replication subsamples and align with prior findings of DMN hypoconnectivity in individuals who are overweight or obese (54). These findings suggest that obesity is associated with perturbations of brain network connections involved in self-referential processing. Crucially, BMI-related decreases in both gFCD within the DMN and lD in corpus callosum were positively correlated, both in Discovery and Replication subsamples, indicating that BMI impacts both functional and structural brain connectivity. This finding aligns with the role of the corpus callosum in facilitating functional connectivity across distributed networks (55). As the ABCD study is longitudinal, monitoring these children over time will enable the assessment of whether a high BMI triggers disruptions in both structural and functional connectivity. It will also help determine whether improvements in connectivity are evident in children who lose weight but not in those who do not. Additionally, examining whether disrupted connectivity in non-overweight or obese children can predict the future development of obesity would suggest that impaired connectivity might serve as a vulnerability factor, increasing the risk for obesity.

In the present study, the fluid and total cognitive composites were lower for obese than normal weight children and decreased in proportion to BMI in obese children, consistent with the negative association between BMI and executive function in ABCD children (7). Children exhibiting lower cognitive composite scores in our study also demonstrated reduced lD in the corpus callosum and lower gFCD in the precuneus. These findings align with our hypothesis that impairments in fluid cognition reflect lower information integration in DMN regions (22) and may be influenced by BMI-related factors. Note that the

lack of associations between the crystalized composite score and BMI is consistent with prior ABCD studies that reported BMI-related decreases for total and fluid cognition, but not for crystallized cognition (56). Though the mechanisms associated with reduced lD and lower gFCD in obese children are unclear they might reflect in part obesity related neuroinflammatory changes (57).

Higher family income was associated with lower BMI, consistent with the negative relationship between household income and BMI in US children that reflects in part the lower costs of obesigenic than healthy foods (58). Income was also positively associated with lD in corpus callosum and with gFCD in DMN regions, consistent with our prior findings (15). Various studies have shown that children from lower income families had worse cognitive performance (59), thinner cortex and smaller cortical surface area and volume (14, 60-65), lower brain activation during working memory (66) and decision-making (67) fMRI tasks, lower fractional anisotropy (68), and have a greater tendency to become obese or overweight in adolescence (69). Together it suggests that excess body weight, which likely reflects multiple factors (improper diet, reduced physical activity, impaired metabolism, genetics, environmental toxins, endocrinological conditions, insufficient sleep, stress, hormonal imbalances, but also likely in some cases, pre-existing executive control dysfunction, among others), contributed to the reduced WM diffusion in corpus callosum and DMN functional connectivity we observed in the children from low-income families.

Here we document partial mediation effects of fALFF in the relationships between both family income and cognitive performance with BMI. Common brain regions that mediated the association between fALFF and obesity for income and cognition included the somatomotor cortex, insula, cingulum, and cerebellum. The identification of insula and the cingulum, regions of the cingulo-opercular network (CON) that is involved in executive control (70), as mediators between both family income and cognitive performance with BMI is in line with the role of the salience network, which is part of the CON in the control of impulsive behavior to high calorie food stimuli in children (71-73). Since preschoolers from low-income families that are obese/overweight have more impulsivity and prefer high calorie foods more than

normal weight preschoolers (74), our CMA findings suggest that higher spontaneous brain activity within regions such as the insula and cingulum may contribute to differences in BMI, potentially through their influence on impulsive behaviors related to food consumption. Furthermore, the mediation of fALFF in somatomotor and cerebellar regions is consistent with their role in motor control, sensory processing, reward integration, impulse regulation, and coordination during eating (75-77).

Though these findings indicate that socioeconomic factors influence BMI partly through their impact on brain activity (fALFF) it is noteworthy that the mediation of fALFF in the indirect effects of cognitive performance on BMI showed a more widespread pattern in the brain than that observed for family income. This indicates that the contribution of regional brain activity to the indirect effects of cognition on the association to BMI goes beyond that mediated through family income. This likely reflects the fact that multiple factors contribute to cognition in children beyond family income including the quality of education, richness of exposures, nutrition, sleep, physical activity and genetics among others (78). Our findings are relevant to public health for they indicate that interventions and policies that provide support to low-income family would improve cognitive performance and brain development as recently shown by a study based on ABCD (79). Our findings also suggest that prevention interventions that support parents on how to improve cognitive skills in children (80) could be beneficial to brain development and reduce the risk for obesity. It also suggests that strengthening the educational system might also help prevent obesity in children.

Our findings reveal a negative correlation between BMI and family income, even among normal-weight individuals. This suggests that the association between BMI and socioeconomic status is not limited to obesity but extends across the entire range of BMI values. Several factors may contribute to this broader relationship. Higher-income families are likely to have better access to healthier food options, opportunities for physical activity, and healthcare resources, all of which support maintaining a healthy weight (81). Additionally, higher educational attainment associated with higher income levels may lead to

360 better knowledge and practices regarding nutrition and health (82). Environmental factors also play a role,
361 as higher-income families often live in neighborhoods with more recreational facilities and safer
362 environments for physical activity (82). Moreover, lower-income families may face higher levels of stress
363 and mental health challenges (83), contributing to weight gain and higher BMI through stress-related
364 eating behaviors and reduced opportunities for physical activity (84). These findings underscore the
365 importance of considering socioeconomic factors in the study of BMI and weight-related health outcomes.
366 Interventions aimed at reducing obesity and improving overall health should consider the broader
367 socioeconomic context and address the disparities in resources, education, and environmental factors
368 that influence BMI.

369 For CMA model 1, the average mediation proportion was higher for fALFF compared to gFCD. This
370 suggests that spontaneous brain activity may have a stronger influence on the relationship between family
371 income and cognitive performance with BMI compared to functional connectivity. While both measures
372 reflect different aspects of brain function, this difference in mediation proportions could reflect the
373 specific roles these brain processes play in the regulation of eating behaviors and metabolic processes.
374 CMA model 1 showed greater mediation proportions compared to CMA model 2, suggesting that family
375 income and cognitive performance influence brain activity and connectivity directly thus increasing their
376 associations with BMI. Our CMA findings also highlight the complex interplay between socioeconomic
377 factors, brain function, and BMI during childhood. While our causal mediation analysis suggests a pathway
378 where impaired cognition influences BMI (CMA model 1), it is important to recognize that the relationship
379 is likely to be bidirectional, with obesity-related metabolic consequences potentially affecting cognitive
380 function (CMA model 2). Furthermore, both BMI and cognitive function could be influenced by other
381 factors, such as socioeconomic status, lifestyle choices, or genetic predispositions. Therefore, our findings
382 should not be interpreted as to conclude that high BMI in youth is solely due to cognitive deficits but
383 instead as part of a complex interplay of multiple factors influencing both cognition and BMI. The direction

of causality in Figure 5D might seem counterintuitive. However, in our analysis, we used total cognition scores as a proxy for cognitive stimulation. Cognitive stimulation, which encompasses various activities that challenge and engage the brain, can play a crucial role in shaping and enhancing brain connectivity, particularly during critical developmental periods. By representing cognitive scores as influencing connectivity, we aim to highlight the dynamic and reciprocal nature of this relationship. Cognitive stimulation, reflected in higher cognitive performance scores, can lead to improvements in brain connectivity, just as robust connectivity can support better cognitive function. This bidirectional relationship underscores the importance of considering both directions of influence in understanding brain-behavior interactions.

Other limitations of our study include the restricted age range of participants, which may limit the applicability of findings to other stages of brain development. Moreover, the underrepresentation of very-low-income families in the ABCD study compared to the broader US population should be noted. While parental education levels align at lower tiers between the ABCD sample and the US population, a relatively higher percentage of parents in the ABCD study attained a Bachelor's degree compared to the US population. The magnitudes of most effects in this study are quite modest, and they achieve statistical significance primarily due to the very large sample size of the ABCD dataset. BMI was also negatively correlated with family income even among normal-weight individuals, whose BMI typically ranged from 15 to 20. This suggests that the association between BMI and family income is not solely driven by obesity but reflects broader socioeconomic influences that affect individuals across the entire BMI spectrum.

In summary, we demonstrate consistent, modest associations between BMI and cognitive performance, family income, spontaneous brain activity and functional and structural brain connectivity in 9-10-year-old children. The association between poor cognitive performance and BMI partially reflects increased spontaneous brain activity in the salience network and somatomotor and cerebellar regions

that is accentuated in children from low-income households. Although our data suggest that low income and impaired cognition influence BMI in part thorugh their effects in brain, it is also likley that these associations are bidirectional. High BMI, with its adverse metabolic effects such as neuroinflammation, likely impacts both the brain and cognition.

Methods

Sex as a biological variable. Findings from this study do not apply exclusively to one sex, as both girls and boys were included in the analysis. Specifically, both girls (n=3,414) and boys (n=3,696) participated in the study, ensuring representation from both sexes. Sex was defined at birth and was determined based on biological characteristics. The ABCD study, from which the data for this study were derived, collected both sex and gender data, ensuring comprehensive data collection practices. There were no significant sex differences in the effect of body mass index on brain connectivity. Consequently, sex was considered as a covariate of no interest in the statistical analysis to account for any potential variability related to sex.

Participants. The multi-site longitudinal ABCD study follows over 11,800 children into early adulthood for ten years with annual lab-based assessments and biennial MRI. Children were excluded if they had medical, neurological, or cognitive problems, poor English-language proficiency, or contraindications for MRI (85).

In the present study, we analyzed baseline neuroimaging and behavioral data from 9,521 children in the ABCD study reported in the 2.0 data release (86) for whom WM diffusion metrics and resting-state fMRI data in Connectivity Informatics Technology Initiative (CIFTI) format were available. In the analysis of functional connectivity, we excluded 560 participants with excessive levels of head motion during resting-state fMRI (>50% of time points with framewise displacement, FD<.5mm), 282 underweight (BMI<5th percentile), and 284 participants missing critical information (BMI, cognitive composite scores, or family income). We restricted the study to African American, Hispanic, and White ethnical groups to minimize variability, and excluded 1,105 participants of Asian (n=162) or mixed (n=943) ethnicity. Thus, the final sample for studies on BMI and resting-state functional connectivity included 7,290 children (3,501 girls and 3,789 boys). The study on structural connectivity metrics was restricted to 4,797 of these participants (2,386 for Discovery and 2,411 for Replication; 2,283 girls and 2,514 boys) who underwent

MRI on Siemens scanners to minimize the variability of DTI metrics across MRI scanners in the ABCD study (87).

Body mass index (BMI). The children's BMI was extracted from the ABCD Youth Anthropometrics data (abcd_ant01.txt), which was downloaded from the National Institute Mental Health Data Archive (NDA; https://nda.nih.gov/). We used the clinical growth charts provided by the National Center for Health Statistics at the Center for Disease Control and Prevention (CDC) to determine BMI percentiles based on age and sex (https://www.cdc.gov/growthcharts/clinical_charts.htm) to determine categories for normal weight (5th percentile < BMI < 85th percentile) and overweight/obese (BMI > 85th percentile).

Behavioral data. We downloaded standard fluid, crystallized and total cognition composite scores from NDA, which were calculated within the NIH Toolbox (23). The uncorrected fluid composite scores were calculated using the following tests: 1) pattern comparison processing speed; 2) list-sorting working memory; 3) picture sequence memory; 4) Flanker; and 5) the dimensional change card sort. The crystallized composite scores were calculated using 6) the oral reading recognition and 7) the picture vocabulary tests. The fluid and crystallized composites were used to calculate the total cognition composite scores.

Family income. The ABCD study surveyed the annual household income using 10 income brackets [1) < $5,000; 2) $5,000–12,000; 3) $12,000–16,000; 4) $16,000–25,000; 5) $25,000–35,000; 6) $35,000–50,000; 7) $50,000–75,000; 8) $75,000–100,000; 9) $100,000–200,000; 10) > $200,000]. This data was downloaded from NDA.

Depression. To assess impairments in functioning due to depression we used the ABCD Parent Diagnostic Interview (abcd_ksad01), which was downloaded from NDA.

MRI data. For functional connectivity analyses, we used the ABCD brain imaging data structure (BIDS) Community Collection (ABCC) (https://collection3165.readthedocs.io/en/stable/), which includes resting-

state fMRI data from 10,038 children that have passed quality assurance (88). ABCD-BIDS used a modified version of the HCP pipeline to accommodate GE, Phillips, and Siemens scanners and head coils from all 21 ABCD sites, which minimizes unwanted variability from differences in MRI scanners. The ABCD imaging procedures were standardized for 3T MRI scanners (Siemens Prisma, Phillips, and General Electric 750 scanners) that were equipped with adult-sized multi-channel coils and capable of performing multiband echo planar imaging (EPI). These procedures were implemented across 21 sites, and further details can be found elsewhere (87, 89). In summary, structural MRI employed 3D T1w inversion-prepared RF-spoiled gradient echo and T2w variable flip angle fast spin echo pulse sequences with 1mm isotropic resolution. Functional MRI (fMRI) data were acquired using T2*-weighted multiband echo planar imaging (EPI) with parameters including TE/TR of 30/800 ms, 2.4 mm isotropic resolution, a flip angle of 52 degrees, 60 slices covering the entire brain, and a multiband slice acceleration of 6 (89). Diffusion MRI data with 1.7mm isotropic resolution were acquired using multiband EPI (90, 91) with slice acceleration factor = 3, five b-values (b = 0, 500, 1000, 2000, and 3000 s/mm^2), and 96 diffusion directions (87). In the ABCD 2.0 data release, a probabilistic method was employed to automatically label all major white matter tracts (92) while excluding gray matter (GM) and cerebral spinal fluid (CSF) voxels (87).

Reproducibility. Participants were split into 3 independent demographically matched subsamples: *Discovery* (N=3,597, girls=1,765), *Replication* (N=3,513, girls=1,649), and *Normality* (N=180; girls=87) using ABCC's "matched group" status, which is based on sociodemographic factors that can impact brain development (age, sex, ethnicity, grade, highest level of parental education, handedness) (88).

Quality Assurance. The automated QA procedures of the ABCD study are described elsewhere (87). Additionally, images underwent correction for scanner-specific gradient distortions and intensity irregularities. Trained evaluators reviewed the images for potential issues like low quality and artifacts such as blurriness, ghosting, or ringing, which might hinder brain segmentation (87).

ABCD-BIDS pipeline. Like the Human Connectome Project (HCP) pipeline, the ABCD-BIDS pipeline comprises 5 consecutive steps: *PreFreesurfer*, performs brain extraction, denoising, and normalization of structural data to a standard template; *Freesurfer*, performs brain segmentation and creates cerebral surfaces with FreeSurfer (87), which has been validated for use in children (93); *PostFreesurfer*, converts brain surfaces into the HCP-compatible CIFTI format; *fMRIVolume*, registers the functional time series to the volumetric standard template; and *fMRISurface*, converts functional time series data to the CIFTI format. Differences between the HCP and ABCD-BIDS pipelines are fully described elsewhere (88). Briefly, the ABCD-BIDS pipeline does not require T2w images and performs the nonlinear registration to the standard atlas in *PostFreeSurfer*, which increases the effectiveness of the registration. Additionally, the ABCD-BIDS pipeline uses ANTS (94) for nonlinear registration which consistently outperforms other nonlinear registration methods (95). In addition, the *fMRISurface* step in the ABCD-BIDS pipeline includes functional connectivity pre-processing that separates true head motion from fictitious motion induced by breathing-related magnetic field changes (96), and performs standard denoising by regressing out time-varying head motion, white matter and CSF signals, and the global signals that may impact group comparisons (97, 98), from both dense (dtseries) and parcellated (ptseries) CIFTI datasets within the 360 cortical partitions (99) and the 19 subcortical partitions obtained from Freesurfer (HCP2016FreeSurferSubcortical_dparc.dlabel.nii), which is also included in the data release of the ABCD-BIDS Community Collection (ABCC).

Head motion. Motion-censoring data, determined using the ABCD-BIDS pipeline, was utilized to eliminate time frames with FD>.5mm. Addressing head motion is crucial in pediatric structural and functional neuroimaging (100). To address this, we also considered subjects' average FD during resting-state fMRI scans as an indicator of their head movement tendencies while in the scanner.

Structural Connectivity. To assess WM integrity from diffusion tension imaging measures of fractional anisotropy (FA), radial diffusivity (rD), longitudinal diffusivity (lD) and mean diffusivity (MD) we used tabulated diffusion imaging metrics, which were downloaded from NDA and are described elsewhere (87).

fALFF and gFCD. The fractional amplitude of low-frequency fluctuations (fALFF) was used to quantify the proportion of resting fMRI signal fluctuations in .01-.1Hz low-frequency band (20), a marker of brain activity (101). Global functional connectivity density (gFCD) mapping (49) was used to quantify the density of functional connections at a given brain coordinate with all other brain coordinates. gFCD was equated to the logarithm of the total number of functional connections, which was computed using Pearson correlation (49). Specifically, two grayordinates were considered functionally connected if their time-varying signals had a correlation R>.6 (21). fALFF and gFCD were mapped at each brain grayordinate (47) from individual time series with N=91,282 grayordinates (102) and a maximum of 1520 time points (20 min) using Matlab 2017b (MathWorks, inc., Natick, MA) and the Biowulf cluster at NIH (https://hpc.nih.gov/).

ROI analysis. Average ROI values within each of the 379 partitions and 28 cerebellar partitions (103), were independently computed for each individual to assess the associations of fMRI metrics (fALFF and gFCD) with cognition and family income. In addition, the edges of individual functional connectomes were averaged independently within the 12 resting-state networks to assess within- and between-network connectivity.

Functional specialization index. To overall functional specialization of the ROIs we used the multi-modal parcellation of the human cerebral cortex (99), which documents the degree of associations with 3 auditory, somatomotor, and visual domains for each ROI. Specifically, the functional specialization index was defined in terms of the absolute differences in specialization between domains S_1=auditory vs

somatosensory; S_2=auditory vs visual; and S_3=somatosensory vs visual as: functional specialization index=max(S_i)-mean(S_i), and was normalized to 1 across 360 atlas partitions (26).

Causal mediation analysis (CMA). The "mediation" package (104) was used to estimate causal mediation effects (105). One thousand bootstrapping samples and a heteroskedasticity-consistent estimator for the covariance matrix were used to estimate the average direct (ADE) and causal mediation (ACME) effects and the mediated proportion.

Statistical analyses. In the independent *Normality* subsample we confirmed the normal distribution of imaging metrics using the Shapiro–Wilk normality test (106) ($W>.98$; $p>.5$). Before statistical analysis we removed site- and scanner-specific differences using grand mean scaling, regressed out effects of head motion and brain volume across participants independently for boys and girls, and removed effects associated with race. Then, a factorial analysis of covariance (ANCOVA) was conducted in MATLAB, independently for the *Discovery* and *Replication* subsamples, to assess the main effects of BMI on the dependent variable Y (fALFF or gFCD) using a sex covariate. In follow-up ROI analyses the effects of BMI, and sex on Y (FA, MD, lD, rD, fALFF, or gFCD) were assessed using ANCOVA in R. We used a false discovery rate threshold $pFDR<.05$ to correct for multiple comparisons across 91,282 grayordinates or 379 ROIs; for the DTI measures we used Bonferroni corrections across 42 major WM bundles in the AtlasTrack (92). Pearson correlation analysis was conducted in R to assess the associations of average brain metrics (Y) within specific ROIs with cognitive composite scores and family income.

Study approval. Local institutional review boards (IRB) at 21 data collection sites across the United States and the IRB at the University of California in San Diego approved the ABCD study (107). Recruitment replicated demographic characteristics of the general US population (108). Children provided written assent for their participation and parents provided written informed consent.

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Data availability

ABCD data are publicly available through the National Institute of Mental Health Data Archive (https://data-archive.nimh.nih.gov/abcd). Supporting data values associated with the main manuscript and supplement material are provided in SupportingData.xlsx.

Acknowledgments

We are thankful to Adam Thomas, PhD, Dustin Moraczewski, PhD, and Eric Earl, BS (National Institute of Mental Health Data Science and Sharing Team) for providing access to the ABCD Community MRI Collection (NDA collection 3165) data on our servers. This study utilized the computational resources of the NIH HPC Biowulf cluster. (http://hpc.nih.gov). This research was supported by the Intramural Research Program of the NIH (Y1AA-3009; ZIAAA000550). Data used in the preparation of this article were obtained from the ABCD Study (https://abcdstudy.org/) and are held in the NIMH Data Archive. The ABCD Study is supported by the National Institutes of Health (NIH). ABCD consortium investigators did not participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

Author contributions

DT and NDV designed the research, DT analyzed data, and DT and NDV wrote the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Tables

Table 1: Characteristics of the *Discovery* and *Replication* samples.

	Discovery	Replication	P
Sample size	3,597	3,513	
Sex (M/F)	1,832/1,765	1,864/1,649	.08†
Age [years]	9.94(.62)	9.94(.62)	.63*
White	2,263	2,196	.98†
Black	546	534	
Hispanic	788	783	
Body mass index [kg/m^2]	19.0(4.0)	19.1(4.1)	.14*
Normal weight	2,436	2,318	.13†
Overweight/Obese	1,161	1,195	
Brain volume [mL]	1,210(113)	1,217(114)	.02*
Obese or overweight (Depressed/Not depressed)	38/692	48/714	.43†
Normal weight (Depressed/Not depressed)	46/1463	47/1374	.77†
Framewise displacement [μm]	118(41)	117(42)	.13*
Siemens	2,392	2,421	.07†
GE	781	691	
Phillips	424	401	
Family income bracket	7.36(2.29)	7.34(2.30)	.64*
Fluid composite score	92.0(10.3)	92.1(10.3)	.74*
Crystalized composite score	86.7(6.7)	86.5(6.8)	.31*
Total composite score	86.7(8.7)	86.7(8.8)	.77*

841 p: 2-sided statistical differences between the *Discovery* and *Replication* samples using 2-sample t-test*

842 or χ^2-test†.

843

Figures.

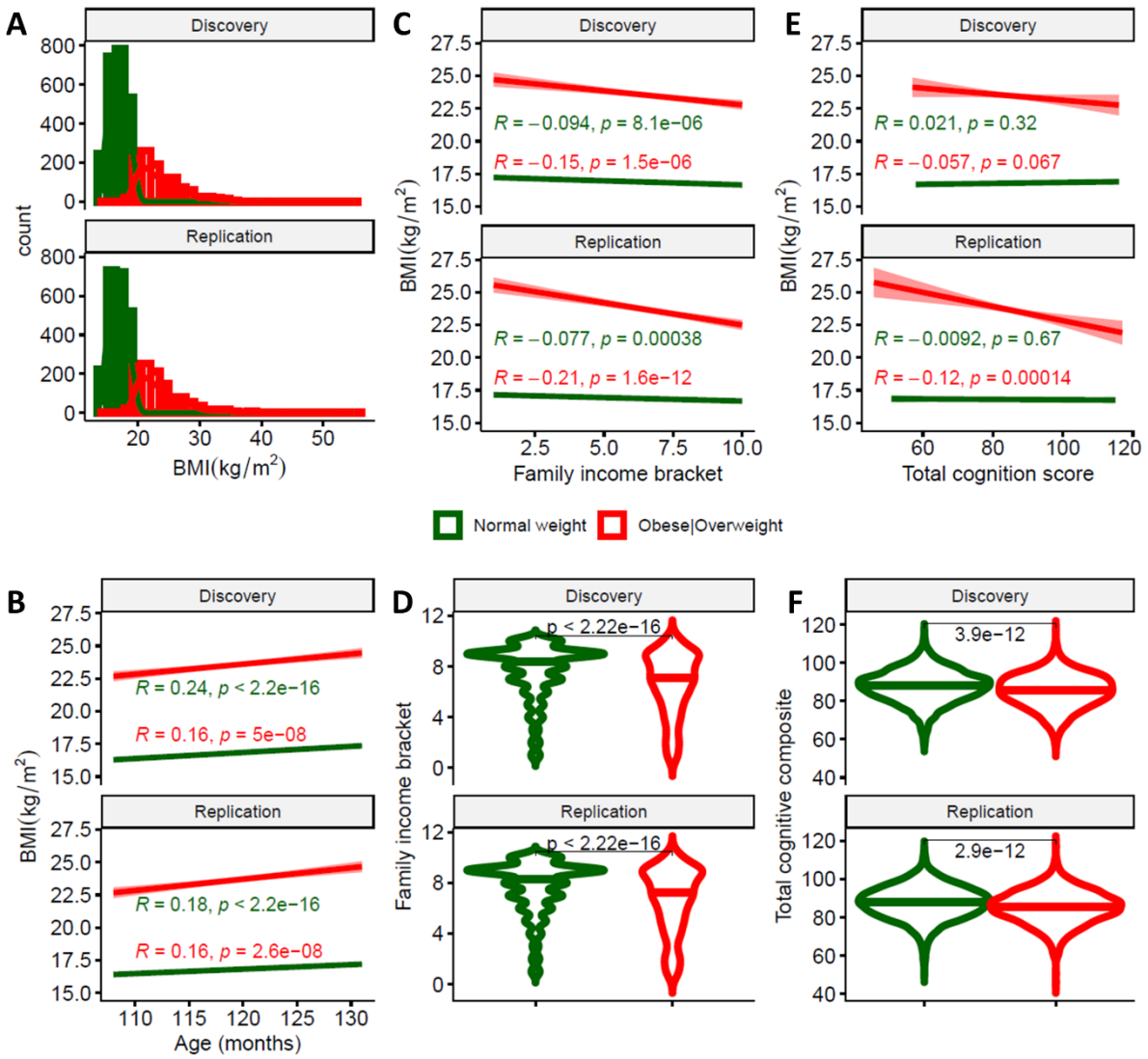


Figure 1. Body mass index (BMI), age, family income and cognition. Distribution of BMI (**A**) and its age-related increases (**B**) among 3,696 boys and 3,414 girls (4,754 normal weight and 2,356 obese/overweight children), and their reproducibility in Discovery (n=3,597) and Replication (n=3,513) subsamples. In obese/overweight children, higher BMI was reproducibly linked to lower family income (**C**) and total cognition scores (**E**). Compared to normal weight, obese/overweight children were more likely to reside in lower income families (**D**) and have lower performance on cognitive tasks (**F**) independently in Discovery and Replication subsamples. BMI percentiles based on age and sex were used to determine weight

categories. Numeric labels are 2-sided p-values reflecting Person correlation analysis (R; b, c, and e) or t-tests (d and f). Shaded areas accompanying line fits are 95% confidence intervals.

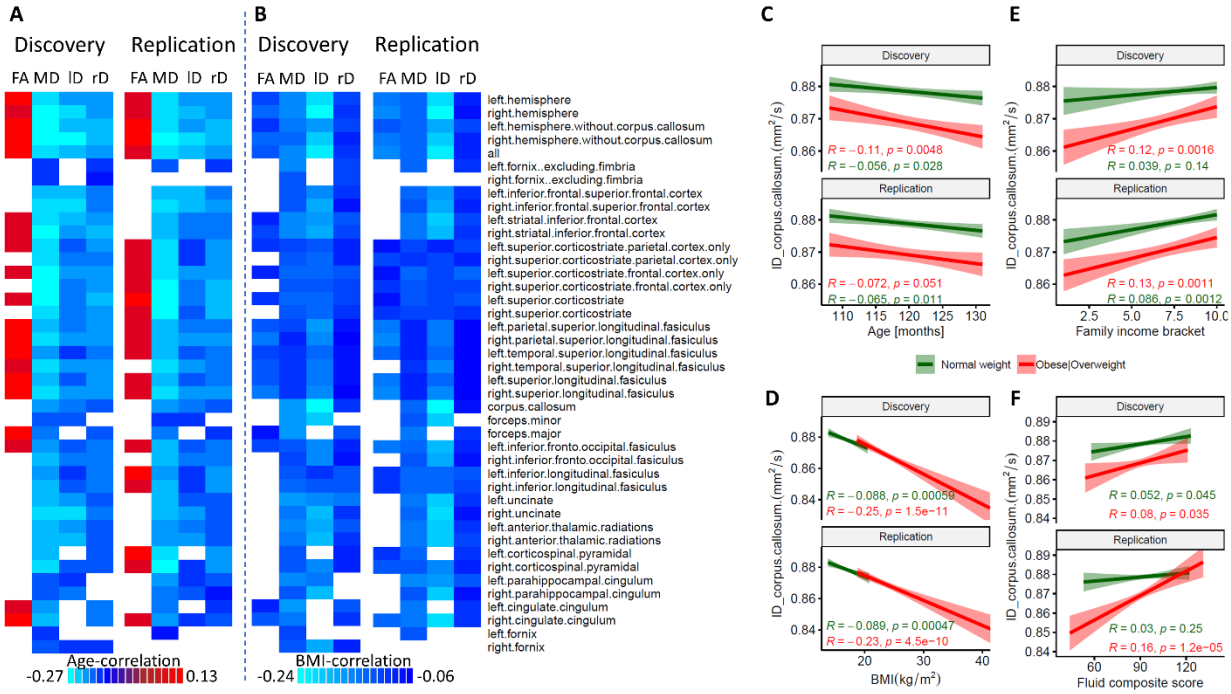
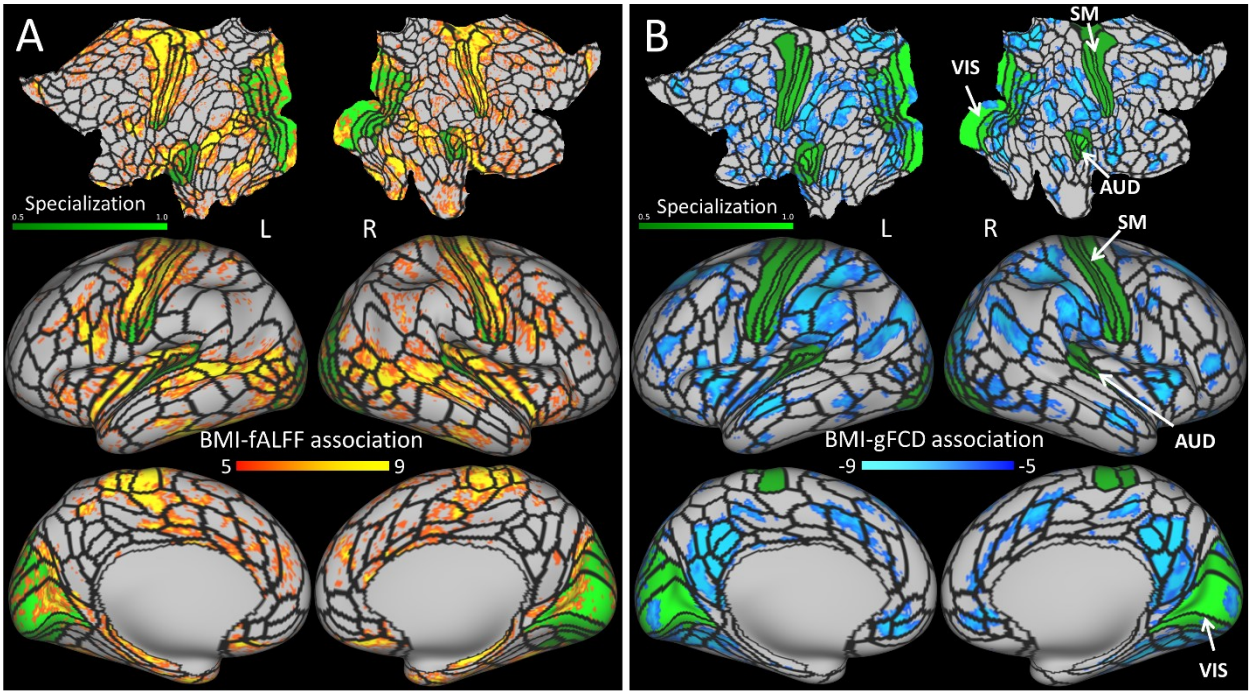
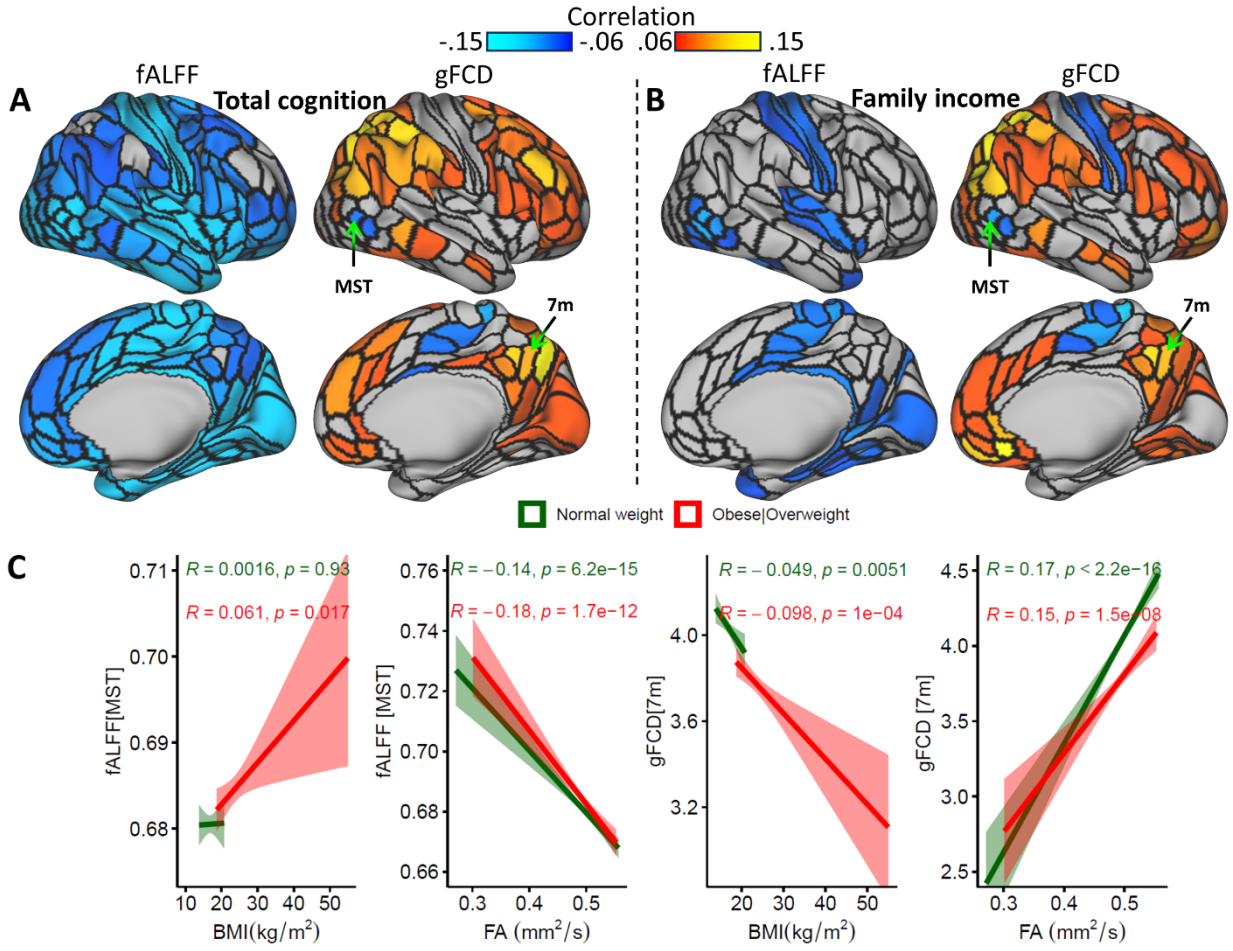


Figure 2. Associations with BMI and age: white matter diffusion. Correlations with age (**A**) and body mass index (BMI; **B**) for brain volume-corrected fractional anisotropy (FA) and mean (MD), longitudinal (lD) and radial (rD) diffusivities in 42 major white matter fiber bundles across Discovery (n=2,386; 1625 normal weight and 761 obese/overweight) and Replication (n=2,411; 1609 normal weight and 802 obese/overweight) subsamples. Linear associations of lD in corpus callosum with age (**C**), BMI (**D**), family income bracket (**E**), and fluid cognitive composite score (**F**). Only data collected in Siemens MRI scanners was used for this analysis. The statistical analysis employed an ANCOVA model with a false discovery rate (FDR) corrected threshold pFDR<.05. BMI percentiles based on age and sex were used to determine weight categories. Shaded areas accompanying line fits are 95% confidence intervals.



865

866 **Figure 3. Associations of BMI with fALFF and gFCD.** Statistical significance (t-score) for the associations of
867 the body mass index (BMI) with the fractional amplitude of low-frequency fluctuations (fALFF; **A**) and
868 global functional connectivity density (gFCD; **B**) across 7110 children, and the score of a functional
869 specialization index highlighting unimodal cortical areas (visual, VIS, auditory, AUD, and somatomotor, SM
870 cortices; see text), rendered on flat (top row) and lateral and medial inflated surfaces (middle and bottom
871 rows) of the left (L) and right (R) cerebral hemispheres. Black lines are the contours of 360 multi-modal
872 partitions of the human cerebral cortex (27). Statistical model: ANCOVA.



873

874 **Figure 4. Associations with cognition, income, and fractional anisotropy (FA).** In the Discovery
875 subsample, higher cognitive composite score (**A**) or family income bracket (**B**) were associated to lower
876 fractional amplitude of low-frequency fluctuations (fALFF) predominantly in insula, cingulum, lateral visual
877 and somatomotor cortices, higher global functional connectivity density (gFCD) in frontoparietal and
878 default-mode network regions, and lower gFCD in somatomotor cortex and lateral occipital areas. **C**)
879 Higher FA, averaged across all white matter fibers in the brain, was associated with lower fractional
880 amplitude of low-frequency fluctuations (fALFF) in the medial superior temporal (MST) area and with
881 higher global functional connectivity density (gFCD) in precuneus (7m), independently for
882 obese/overweight (n=2,356; red) and normal weight (n=4,754; green) children. Higher body mass index
883 BMI was associated to lower gFCD in precuneus, independently across weight categories, and to higher

fALFF only in obese/overweight children. Right cerebral hemisphere. Black contours delineate the borders of 180 ROIs in the right cerebral hemisphere. BMI percentiles based on age and sex were used to determine weight categories. Shaded areas accompanying line fits are 95% confidence intervals.

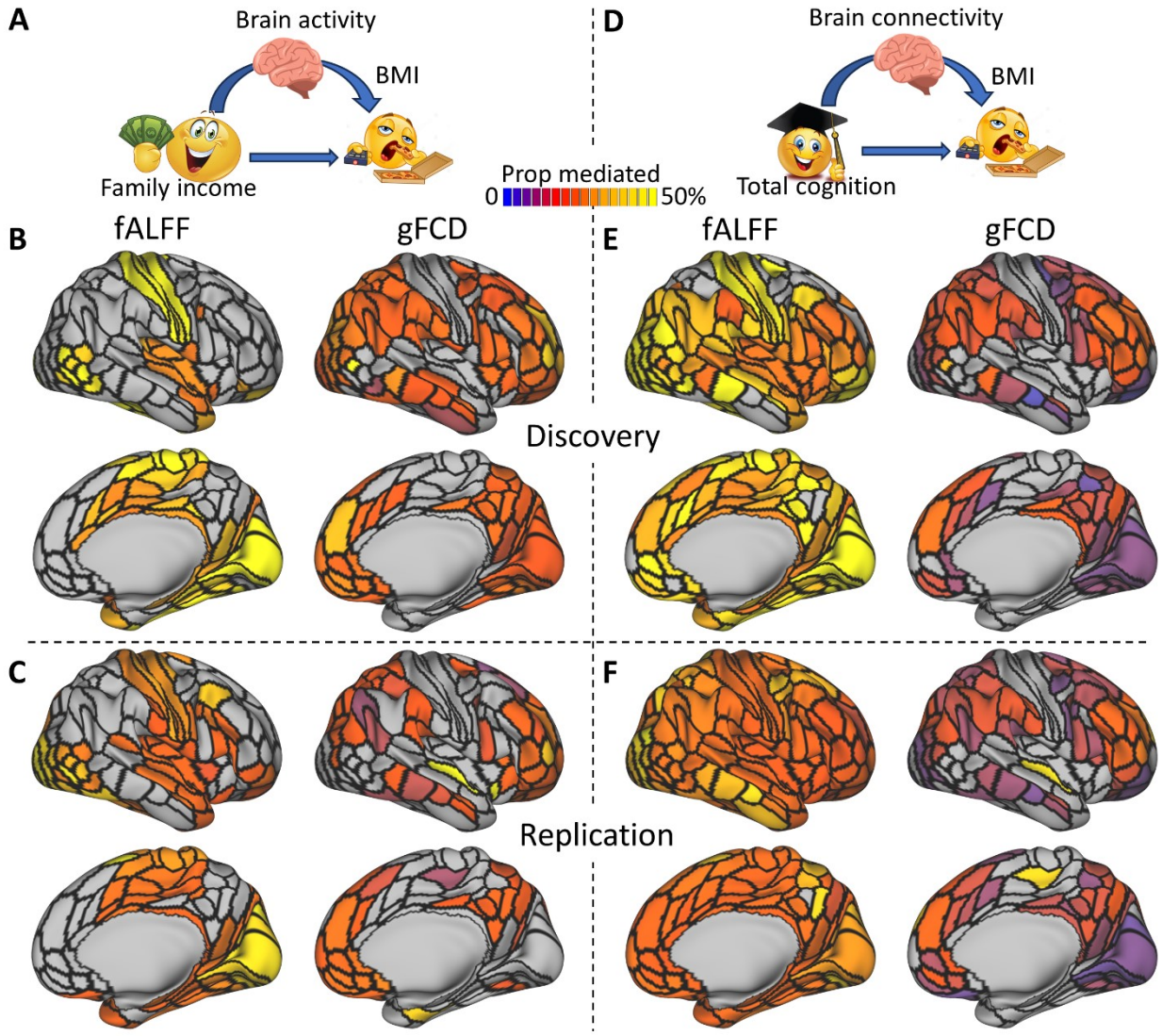


Figure 5. Causal mediation analysis (CMA; Model 1). Proportion of the total effects of family income (**A-C**) or cognitive performance (**D-F**) on the association with body mass index (BMI) that is mediated by the fractional amplitude of low-frequency fluctuations (fALFF), or global functional connectivity density (gFCD) overlaid on lateral and medial surfaces of the right cerebral hemisphere for the Discovery (n=3,597

892 children) and the Replication sample (n=3,513 children). Black contours delineate the borders of 180 ROIs

893 in the right cerebral hemisphere. Threshold $P_{ACME} < .001$.

894