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FTO variation and early frontostriatal brain development in children

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Abstract

Objective: Common obesity-associated genetic variants at the *FTO* locus have been associated with appetitive behaviors and altered structure and function of frontostriatal brain regions. We aimed to investigate the influence of *FTO* variation on frontostriatal appetite circuits in early life.

Methods: Data were drawn from RESONANCE, a longitudinal study of early brain development. Growth trajectories of nucleus accumbens (NAcc) and frontal lobe volumes, and total gray matter and white matter volume (GMV, WMV), by risk allele (A) carrier status on *FTO* SNP rs9939609 were examined in 228 children (102 F, 126 M), using MRI assessments obtained from infancy through middle childhood. We fit functional concurrent regression models with brain

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volume outcomes over age as functional responses, and *FTO* genotype, sex, BMIz, and maternal education included as predictors.

Results: Bootstrap pointwise 95% confidence intervals for regression coefficient functions in the functional concurrent regression models showed the AA vs. TT group had greater NAcc volume (adjusted for total brain volume) in the 750–2250 days (2–6 years) interval.

Conclusions: Our findings suggest common genetic risk for obesity is associated with differences in early development of brain reward circuitry, and argue for investigating dynamic relationships between genotype, brain, behavior, and weight throughout development.

1. Introduction

Common intronic single nucleotide polymorphisms (SNPs) on the fat mass and obesity-associated *FTO* gene increase obesity risk, with individuals who are homozygous for the risk allele (AA) of rs9939609 being at higher risk than heterozygotes (AT) and those with no risk alleles (TT) in both adulthood and childhood (1,2). Further, the association between *FTO* genotype and BMI has been shown to progressively increase between ages 4 and 11, supporting a role for expression of *FTO* in the increasing heritability of adiposity over childhood (3). The functional pathways underlying the effects of common *FTO* variation on body weight are not well understood, but observational studies in children support appetitive mechanisms. For example, high-risk genotypes on *FTO* SNP rs9939609 have been associated with obesogenic eating behaviors including lower satiety responsiveness (4), greater food responsiveness (5,6), greater emotional overeating (5), greater perceived loss of control over eating (7), and increased energy intake in behavioral paradigms including the eating in the absence of hunger (EAH) test (8–10), and effects of *FTO* variation on child weight show partial mediation by measures of appetite (4,11).

A growing body of preclinical studies and clinical Magnetic Resonance Imaging (MRI) studies in adults and children suggest that obesity-associated appetitive behaviors are orchestrated by a network of distributed brain regions that include frontostriatal circuits subserving self-regulatory capacities and motivated behavior (12–14). Work in animal models has established that mesolimbic structures including the nucleus accumbens (NAcc) and orbitofrontal cortex (OFC) contain localized hedonic hot and cold spots that upon stimulation can enhance or suppress ‘liking’ reactions to palatable foods, while in the mesocorticostriatal ‘wanting’ circuitry, dopamine stimulation generates cue-triggered incentive salience, increasing motivation to seek and consume palatable food rewards (15). In addition, models of diet-induced obesity have demonstrated micro-structural differences in NAcc that are consistent with a neuro-inflammatory response and act to influence food seeking behavior (16,17).

Consistent with preclinical work implicating the NAcc, meta-analyses of studies of adults and adolescents and analyses of the large-scale UK Biobank dataset in adults have shown that greater NAcc volume is associated with greater BMI (18). Importantly, this relationship is dependent on age with younger participants showing a positive relationship but older adults showing a negative relationship (18). These findings are in line with other reports of greater NAcc volume with greater adiposity in adolescents (19,20), and with longitudinal

studies of 9-11-year-olds showing that cellular density in the NAcc predicts increases in waist circumference (21) and mediates the relationship between dietary fat consumption and waist circumference (22). Together these phenomena suggest potential changes over development such that increased NAcc volume early in life might increase obesity risk via appetitive mechanisms, then neuroinflammatory effects of prolonged exposure to high fat diets and adiposity may result in observations of decreased NAcc volume with increased BMI at older ages.

Human imaging studies have been perhaps most concordant in reporting volume reductions in frontal cortex with higher BMI. Cross-sectional analyses of data in 9-12-year-olds from the large US ABCD cohort have demonstrated that greater BMIz is associated with lower cortical thickness across prefrontal cortex (PFC) (23,24), as well as with reduced volumes in medial OFC and medial superior frontal gyrus (25), and lower volume, cortical thickness and surface area in middle frontal gyrus (26,27) and dorsolateral PFC (26), while analyses of non-US pediatric cohorts have also reported weight-associated reductions in frontal lobe volume (28,29).

Genetic variation at the *FTO* locus has also been linked with altered structure and function within NAcc and frontal cortex in a handful of studies in adults, adolescents, and school-aged children. Studies of older adults have observed reduced frontal lobe volumes among risk allele carriers, which were in turn associated with higher BMI (30), and also lower NAcc volumes independent of BMI (31). In contrast, a study of 9-12-year-olds found that those with the *FTO* rs9939609 AA/AT (vs. TT) genotype had larger NAcc volumes (32), as well as greater NAcc responses to food commercials (32) independent of BMI. Of note, studies of adults have also found some evidence for greater striatal food cue responses among risk allele carriers (33), as well as lesser responses in PFC in a fed condition (34). Together the findings reviewed above suggest frontostriatal brain circuits influence eating behavior and weight and may mediate effects of common genetic variation at the *FTO* locus.

Identifying effects of *FTO* on early developing appetite circuitry could illuminate neurobehavioral mechanisms as well as support and inform on early intervention strategies. However, to date we are not aware of either cross-sectional or longitudinal studies of effects of *FTO* variation on appetitive circuits in children under 5 years. Therefore, based on evidence that high-risk genotypes on *FTO* SNP rs9939609 have been associated with obesogenic eating behaviors (4–10) in pediatric populations, we aimed for the current study to test the pre-defined hypothesis that variation on *FTO* SNP rs9939609 would be associated with differences in early structural development of appetitive brain circuits, using currently available longitudinal Magnetic Resonance Imaging (MRI) data from the RESONANCE cohort, collected in children from infancy through middle childhood. Although multiple brain regions are implicated in appetite regulation (35) and variation at the *FTO* locus (30), we confined this preliminary, hypothesis-driven investigation to frontostriatal circuits due to well-documented involvement in appetite regulation as supported by preclinical and large-scale human studies (18–20,23,24,28,29). Specifically, our primary aim was to examine differences in growth trajectories of i) NAcc and ii) total frontal lobe volume by *FTO* genotype (SNP rs9939609), adjusting for total brain volume. Since large pediatric studies have reported reductions in total gray matter volume and total white matter volume

by body weight (27,29), and there is some evidence for effects of *FTO* variation on global brain volume in adolescents (36), we also evaluated differences in total gray matter volume and total white matter volume.

2. METHODS

2.1 Participants

Brain imaging data presented here was collected in the RESONANCE cohort, an ongoing longitudinal study of early brain and cognitive development in children from infancy through childhood. Research ethics oversight was provided by the host institutions, including the Brown University and Lifespan institutional review boards. For all children, written informed consent was obtained from their parents or legal guardians. Details of the study have been described elsewhere (37,38). In brief, participants are recruited either during pregnancy or when the child is 0–5 years. As a study of neurotypical development, infants and young children with major developmental disorders are excluded during enrollment. Children then undergo multi-modal MRI scanning and other assessments at 6-month increments from the time of recruitment until 2 years of age, and yearly thereafter. The assessment battery includes anthropometric assessments and tests of cognitive and behavioral functioning. Collection of biospecimens includes saliva for DNA extraction. For the current analysis we included data collected up until 8th November 2019. Of the n=960 children who had participated in RESONANCE up to this date, n=226 had complete data (i.e., 419 MRI assessments) on all of our variables of interest including processed cleaned brain volume data, *FTO* genotype, age, sex, maternal education and BMI-z scores. The difference in number between the analysis sample and the complete sample is largely due to batch processing of MRI data and genetic samples as well as staged introduction of measures into the larger study (e.g. collection of genetic data, and BMIz data). Importantly, the analysis sample did not differ significantly from the larger sample on variables that were available for a large number of the children, i.e. child age (available n=960/960), sex (available n=960/960), maternal education (available n=829/960) and BMIz score (available n=832/960). There was also no evidence for differences between children in the analysis sample and children in the larger sample who had data on *FTO* genotype (available n=495/960). We are therefore reasonably confident that our analysis sample is representative of the larger, socioeconomically diverse, RESONANCE cohort.

2.2 MRI image acquisition

T1 weighted anatomical data for this study were acquired on a 3T Siemens Trio scanner with a 12-channel head RF array using a magnetization-prepared rapid acquisition gradient echo scan of each child with an isotropic voxel volume of 1.4 × 1.4 × 1.4 mm3. Sequence-specific parameters were: TE = 6.9 ms; TR = 16 ms; inversion preparation time = 950 ms; flip angle = 15°; BW = 450 Hz/Pixel. The acquisition matrix and field of view were varied according to the child's head size to maintain a constant voxel volume and spatial resolution across all ages. To achieve successful scanning without the use of sedatives, scans for younger participants were scheduled around the child's natural sleep time. Once asleep, the child was transferred from one of the napping beds. These beds include a bottom layer of custom-made plexiglass that enable the child to be placed asleep onto the scanner bed.

Custom-made padding is employed inside the bore to quiet the scanning noise, custom headphone pieces play soothing rain sounds, and additional padding is used to help the child remain in a fixed position. At least one research assistant accompanied the child into the scanner.

2.3 Image Analysis

For image processing, a combination of linear and nonlinear registration was used to create a representative age-specific template using the ANTs package (39). After age-specific templates were created, a single flow from each age to the 12-month template was estimated and a final warp from the 12-month template to standard adult MNI space was performed. For each infant/ child brain image, we then calculated the warp from their native T1w image space to their nearest-in-age template. Using the resulting warps (native → nearest age template → 12-month template → MNI template), we could move the standard adult brain atlas to the space of an individual infant in a single step. In this case, we used the Harvard-Oxford brain atlas to provide a coarse-grained parcellation of individual brains into subcortical regions (e.g., NAcc) and total gray and white matter volumes as included as part of the FSL package (40). Total left and right hemisphere volumes were derived for total white and gray matter, and for frontal lobe and NAcc volumes (41). NAcc and frontal lobe volumes (mm^3) used in longitudinal models were adjusted for total brain volume by dividing by the sum of total gray and white matter. This method was adopted rather than adjusting for total intracranial volume as more conventionally done in adults in order to avoid the impact of variation of small ventricle volumes within the neonatal brain on total brain volume, as well as to avoid possible confounding by sex differences in total brain volume (42).

2.4 Sample collection and genotyping

Saliva was collected from participants using Oragene (DNA Genotek, Ottawa, ON, Canada) saliva collection kits. DNA was extracted with the supplier's isolation kit (DNA Genotek's PT-L2P-5). Sample yield and purity were assessed spectrophotometrically using the NanoDrop ND-1000 (ThermoScientific, Wilmington, DE, USA). Children were genotyped for the A/T rs9939609 SNP of *FTO* using Multi-Ethnic Global Array (MEGA, >1.7 million markers) run on an Illumina iScanSystem (Illumina, San Diego, CA, USA). Initial genotype definitions were based on auto-clustering of all samples that had a call rate >0.98 using GenomeStudio (Illumina). To capture population stratification, we calculated the first 10 principal components and eigenvalues using PLINK v1.9 (--pca) with default minor allele frequency (--maf) and call rate (--geno) filters. Using the computed eigenvalues a scree plot was then generated and inspected, supporting the inclusion of the first 3 principal components in our analysis models.

2.5 Statistical analysis

Our primary aim was to compare i) NAcc and ii) frontal lobe volumes adjusted for total brain volume across the three *FTO* groups (TT, AT, and AA). In addition, we compared total gray matter volume and total white matter volume, across the three *FTO* groups (TT, AT, and AA). Comprehensive details of our statistical models in the context of functional data analysis(43,44) can be found in Supplementary Materials. In brief, we fit functional concurrent regression models with brain volume outcomes over(45,46) the age domain

as functional responses, *FTO* genotype, sex and maternal education, 3 genetic principal components (PCs) as scalar predictors, and BMIz over the age domain as a functional predictor. For *FTO* genotype the TT group was treated as the baseline group and the AT and AA groups as dummy indicator variables. For sex, male was used as the baseline category with female as the dummy variables. For maternal education (used as a proxy for SES), level 0 (no university/college education) was treated as the baseline group and level 1 (university/college education) the dummy variable. Bootstrap pointwise 95% confidence intervals (pointwise at every age) for the regression coefficient functions in the concurrent regression model were used to test if the growth trajectories of volume outcomes were statistically significantly different between the three *FTO* groups, adjusting for sex, maternal education, and BMIz trajectories. The inclusion of the value 0 in the bootstrap pointwise 95% confidence interval indicates a statistically non-significant effect at that particular age, with a 5% level of significance. Conversely, the exclusion of the value 0, indicates a statistically significant effect at that age. Since we confined our main tests to just two brain regions of interest in this preliminary analysis of the accruing RESONANCE sample, we did not apply correction for multiple comparisons. An implementation of these statistical methods is available in the R package "fdaconcur'(47), with its current version on GitHub available at: https://github.com/functionaldata/tFDAconcur

3. RESULTS

3.1 Participant characteristics

For the present analysis we included data from 228 typically developing children, of whom 46 (20%) children were homozygous for the risk (A) allele on *FTO* SNP rs9939609 (AA), 111 (49%) were heterozygous for the risk allele (AT), and 71 (31%) had no risk alleles (TT). Table 1 provides sample characteristics. Chi squared analyses for categorical variables and one-way ANOVAs for continuous variables revealed no significant differences in child sex, child BMIz, child weight group based on World Health Organization (WHO) reference data, maternal education, child race, child age at included timepoints, or number of timepoints contributed to the analysis per child, by *FTO* genotype. Figure 1 gives histograms for the number of repeated measurements per child and age at visit.

3.2 Brain volume trajectories by *FTO* genotype

Results of functional concurrent regression models with NAcc and frontal lobe volumes adjusted for total brain volume over the age domain as functional responses are described below and depicted in Figures 2 and 3. Results of functional concurrent regression models with total gray and white matter volumes (mm^3) over the age domain as functional responses revealed no significant differences by *FTO* genotype and are described in more detail in Supplementary Materials and depicted in Supplementary Figures s1 and s2. We note that although our datasets included a small number of participants with observations out to age 5476 days, data sparsity beyond age 3500 days made corresponding estimates unstable and the results unreliable. We thus present all results over the age domain 0–3500 days and interpret patterns of data exclusively within this age interval.

3.2.1 Nucleus accumbens volume trajectories by *FTO* genotype—

Results of functional concurrent regression models with NAcc volume (as a fraction of total brain volume) over the age domain as a functional response are depicted in Figure 2. For the AT vs. TT comparison (Figure 2A), the estimated regression coefficient function takes values very close to zero at all ages up to 3500 days. At a confidence coefficient of 95%, the effect of AT on NAcc volume growth trajectory is not significantly different from that of the baseline *FTO* group TT at any age. AA vs TT (Figure 2B) comparison revealed that the bootstrap pointwise 95% confidence band did not include the value 0 in the age window 750–2250 days (2 to 6 years) and the estimated regression coefficient function based on the fitted concurrent functional model takes positive values all along the age axis. This indicates that adjusting for all other relevant predictors (sex of the child, mother's education level as a proxy for SES indicator, BMI of the child, first 3 genetic principal components), then a child in the obesity risk group AA tends to have higher NAcc volume (adjusted for total brain volume) than a child in the obesity risk group TT in the age interval of 2 to 6 years.

3.2.2 Frontal lobe volume trajectories by *FTO* genotype—

Results of functional concurrent regression models with frontal volume (as a fraction of global brain volume) over the age domain as a functional response are depicted in Figure 3. As shown for the comparison of AT vs. TT (Figure 3A), and the comparison of AA vs. TT (Figure 3B), at a confidence coefficient of 95%, NAcc volume growth trajectories for the AT and the AA group are not significantly different from that of the baseline *FTO* group TT at any age.

4. DISCUSSION

We here present the results of initial analyses investigating growth trajectories of frontostriatal brain regions, as well as of total gray matter volume and total white matter volume, in children at increased genetic risk for obesity based on common variation at the *FTO* locus. Using a unique dataset of 419 structural MRI assessments collected from infancy through childhood in 228 children participating in RESONANCE, an ongoing longitudinal study of early brain development, we found that children with two compared with zero risk alleles on *FTO* SNP rs9939609 demonstrated greater volume in the NAcc, adjusted for total brain volume, in the age interval of 750–2250 days (2–6 years). These effects were independent of child sex, maternal education (used here as a proxy for family socio-economic status) and child BMIz trajectories. We did not find evidence that total gray matter volume or total white matter volume differed by *FTO* genotype.

Our finding of greater NAcc volume in children at increased genetic obesity risk based on *FTO* variation, independent of current body weight, builds upon a similar observation in a previous study of 9-12-year-olds (32) by demonstrating that this phenomenon is observable as early as 2 years of age. Since the NAcc plays a key role in food motivation (15) and studies have found that greater NAcc volume in adolescents and younger adults is associated with greater BMI (18–20) while NAcc cytoarchitecture predicts weight gain in childhood (21,22), it is possible that greater NAcc volumes in the AA group at this early developmental stage may predict excess intake and weight gain later in development. We are unable to speculate based on the current analysis on biological mechanisms underlying impacts of *FTO* variation on NAcc volume in young children. However, *FTO* variation influences

eating behavior (4–11) and exposure to high-fat diets in animals has been associated with micro-structural differences in NAcc potentially attributable to neuroinflammation-induced increases in glial cells (16,17,48), so we cannot rule out dietary pathways.

Our models revealed significantly greater NAcc volume for children with the AA genotype by age 2 years, in terms of pointwise (not simultaneous) comparisons, but it is important to note that this was no longer the case beyond age 6 years. Notably, this does not mean that such an effect does not exist in this age range as failure to detect it could be due to insufficient sample size). It is therefore possible that our findings reflect a pattern whereby this striatal reward region demonstrates accelerated growth in children with higher genetic obesity risk but after 6 years of age, the brain returns to a similar growth trajectory as TT group, perhaps via compensatory mechanisms. During this age range, brain maturation is defined by microstructural processes such as oligodendrogenesis and synaptogenesis, which slow down drastically after age 6, triggering synaptic pruning to follow (for review, (49)). These microstructural processes are paralleled by significant socio-emotional and cognitive developments (49) which critically involve the NAcc (for review see (50)). Thus, early childhood spanning ages 2 to 6 might represent a sensitive period for NAcc development, after which genetically-driven increases in NAcc volume may be eliminated due to synaptic pruning. We also note that although volume differences by genotype were not apparent in our sample after age 6 years, our current analysis does not speak to NAcc microstructure or function, both of which could still show differences by *FTO* genotype. For example, a recent longitudinal study suggested a reciprocal relationship between NAcc microstructure assessed after age 6 years, and later childhood weight gain (22). We further note that our analysis sample was relatively small and replication in a larger sample as the RESONANCE cohort continues to accrue (as well as replication in other longitudinal cohorts beginning in early life) will be crucial to establish the reliability and generalizability of the 2–6y finding we report. We additionally note that our models only extended reliably out to 3500 days (9.5 years) of age and we will be unable to investigate whether there is further differentiation of NAcc growth by *FTO* genotype at later ages until more data is obtained in the current cohort.

Notably we did not observe an effect on NAcc volume among individuals carrying just one risk allele on *FTO* SNP rs9939609. Our assumption is that for this particular phenomenon, two risk alleles were required for an observable effect (haploinsufficiency). As the mechanism for the effects of *FTO* SNP rs9939609 has not yet been established we are unable to speculate further than this. However, we note that studies of the effect of *FTO* SNP rs9939609 on eating behavior have similarly observed effects in homozygotes but not heterozygotes. For example, children with two *FTO* A alleles exhibit low responsiveness to satiety cues (4). Similarly, another study showed that children with two copies of AA had greater odds of scoring on food responsiveness (6).

Growth trajectories of frontal lobe volume, and of total gray matter volume and total white matter volume, did not differ by *FTO* genotype in the current study. Our analysis sample was relatively small and our longitudinal data quite sparse, so larger datasets may be needed to fully capture such relationships. It is also possible that, although frontal lobe volume trajectories did not differ, trajectories of specific frontal regions with relevance to obesity

(e.g. OFC, PFC) may have differed in opposing ways that were averaged out over our large frontal lobe region of interest. However, since striatal reward regions mature earlier than frontal regions implicated in self-regulation (51), it is also possible that impacts of genetic obesity risk are expressed preferentially in reward circuitry in early childhood, with impacts on frontal circuits not appearing until later in development.

Our results should be interpreted in light of the limitations of our data. First, we do not currently have sufficient overlapping data on child eating behavior, or prospective anthropometric data, to determine the functional consequences of the NAcc volume differences we observed. Second, since we took the conservative approach of confining our investigation to two regions of interest, we cannot rule out the possibility of differences in other brain regions e.g. regions that have demonstrated functional differences by *FTO* genotype in 5–11 year-olds (anterior insula (52) and 14–17 year-olds (putamen and PFC (53)). Third, although we chose *FTO* SNP rs9939609 due to evidence for frontostriatal involvement and a role in appetite regulation, polygenic risk scores (PRS) for obesity (54) may in practice incorporate many genetic variants with small effects on frontostriatal appetite circuits and may thus demonstrate larger effects on the brain than were captured here. Whole genome sequencing and investigation of other *FTO* SNPs could also shed further light on genetic effects on early development of brain appetite circuits. Fourth, since BMI may result indirectly from brain differences, it is debatable whether BMI should be factored out in models of *FTO* effects. However, we note that in models that did not include BMI (not presented) we saw very similar findings in the NAcc. Fifth, our findings are based on pointwise not simultaneous inference and were not adjusted for multiple testing. Lastly, we acknowledge that the adjusted volume differences we observed were small. To understand the meaning of the observed NAcc difference by *FTO* genotype it will be necessary to investigate potentially dynamic relationships between *FTO* genotype, brain, behavior, and weight throughout development within the RESONANCE sample but also within other cohorts containing similar data for the purpose of replication.

5. CONCLUSION

Our findings suggest genetic risk for obesity may be associated with differences in the early development of brain reward regions that could potentially influence weight gain later in development. More generally, they highlight the importance of investigating potentially dynamic relationships between genotype, brain, behavior, and weight throughout development. Further investigation of how brain appetite circuitry develops in early life in children at raised obesity risk may illuminate neurobehavioral mechanisms of obesity risk and potentially aid the development of neurobehaviorally-targeted interventions to prevent excess weight gain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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7. REFERENCES

1. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science (80-) [Internet]. 2007/04/12. 2007 May 11;316(5826):889–94. Available from: https://pubmed.ncbi.nlm.nih.gov/17434869
2. Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, et al. Variation in *FTO* contributes to childhood obesity and severe adult obesity. Nat Genet. 2007 Jun;39(6):724–6. [PubMed: 17496892]
3. Haworth CMA, Carnell S, Meaburn EL, Davis OSP, Plomin R, Wardle J. Increasing heritability of BMI and stronger associations with the *FTO* gene over childhood. Obesity (Silver Spring). 2008 Dec;16(12):2663–8. [PubMed: 18846049]
4. Wardle J, Carnell S, Haworth CMA, Farooqi IS, O'Rahilly S, Plomin R. Obesity associated genetic variation in *FTO* is associated with diminished satiety. J Clin Endocrinol Metab. 2008;93(9):3640–3. [PubMed: 18583465]
5. Obregón Rivas AM, Santos JL, Valladares MA, Cameron J, Goldfield G. Association of the FTO fat mass and obesity-associated gene rs9939609 polymorphism with rewarding value of food and eating behavior in Chilean children. Nutrition. 2018 Oct;54:105–10. [PubMed: 29778907]
6. Velders FP, De Wit JE, Jansen PW, Jaddoe VW V, Hofman A, Verhulst FC, et al. *FTO* at rs9939609, food responsiveness, emotional control and symptoms of ADHD in preschool children. PLoS One. 2012;7(11):e49131. [PubMed: 23155456]
7. Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, et al. The *FTO* gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nutr. 2009;90(6):1483–8. [PubMed: 19828706]
8. Cecil JE, Ph D, Tavendale R, Ph D, Watt P, Ph D, et al. An Obesity-Associated *FTO* Gene Variant and Increased Energy Intake in Children. N Engl J Med. 2008;359:2558–66. [PubMed: 19073975]
9. Wardle J, Llewellyn C, Sanderson S, Plomin R. The *FTO* gene and measured food intake in children. Int J Obes. 2009;33(1):42–5.
10. Gilbert-Diamond D, Emond JA, Lansigan RK, Rapuano KM, Kelley WM, Heatherton TF, et al. Television food advertisement exposure and *FTO* rs9939609 genotype in relation to excess consumption in children. Int J Obes (Lond). 2017 Jan;41(1):23–9. [PubMed: 27654143]
11. Emond JA, Tovar A, Li Z, Lansigan RK, Gilbert-Diamond D. *FTO* genotype and weight status among preadolescents: Assessing the mediating effects of obesogenic appetitive traits. Appetite. 2017 Oct;117:321–9. [PubMed: 28712975]
12. Thapaliya G, Sadler JR, Jansen E, Carnell S. Obesity and appetite: Evidence for a neurobehavioral model of obesity risk and maintenance [Internet]. Vols. 1–3, Encyclopedia of Behavioral Neuroscience: Second Edition. Elsevier; 2021. 347–359 p. Available from: 10.1016/B978-0-12-819641-0.00142-0
13. Sadler JR, Thapaliya G, Ranganath K, Gabay A, Chen L, Smith KR, et al. Paediatric obesity and metabolic syndrome associations with cognition and the brain in youth: Current evidence and future directions. Pediatr Obes. 2023 May;e13042. [PubMed: 37202148]
14. Carnell S, Thapaliya GJE and CL. Biobehavioral susceptibility for obesity in childhood: behavioral, genetic and neuroimaging studies of appetite. Physiol Behav (Under Revis.

15. Morales I, Berridge KC. “Liking” and “wanting” in eating and food reward: Brain mechanisms and clinical implications. Physiol Behav. 2020 Dec;227:113152. [PubMed: 32846152]
16. Décarie-Spain L, Sharma S, Hryhorczuk C, Issa-Garcia V, Barker PA, Arbour N, et al. Nucleus accumbens inflammation mediates anxiodepressive behavior and compulsive sucrose seeking elicited by saturated dietary fat. Mol Metab. 2018 Apr;10:1–13. [PubMed: 29454579]
17. Gutiérrez-Martos M, Girard B, Mendonça-Netto S, Perroy J, Valjent E, Maldonado R, et al. Cafeteria diet induces neuroplastic modifications in the nucleus accumbens mediated by microglia activation. Addict Biol. 2018 Mar;23(2):735–49. [PubMed: 28872733]
18. García-García I, Morys F, Dagher A. Nucleus accumbens volume is related to obesity measures in an age-dependent fashion. J Neuroendocrinol. 2020 Dec;32(12):e12812. [PubMed: 31758711]
19. Kakoschke N, Lorenzetti V, Caeyenberghs K, Verdejo-García A. Impulsivity and body fat accumulation are linked to cortical and subcortical brain volumes among adolescents and adults. Sci Rep. 2019;9(1):1–11. [PubMed: 30626917]
20. Perlaki G, Molnar D, Smeets PAM, Ahrens W, Wolters M, Eiben G, et al. Volumetric gray matter measures of amygdala and accumbens in childhood overweight/obesity. PLoS One. 2018;13(10):1–17.
21. Rapuano KM, Laurent JS, Hagler DJ, Hatton SN, Thompson WK, Jernigan TL, et al. Nucleus accumbens cytoarchitecture predicts weight gain in children. Proc Natl Acad Sci U S A. 2020;117(43):26977–84. [PubMed: 33046629]
22. Rapuano KM, Berrian N, Baskin-Sommers A, Décarie-Spain L, Sharma S, Fulton S, et al. Longitudinal Evidence of a Vicious Cycle Between Nucleus Accumbens Microstructure and Childhood Weight Gain. J Adolesc Heal [Internet]. 2022;70(6):961–9. Available from: 10.1016/j.jadohealth.2022.01.002
23. Laurent JS, Watts R, Adise S, Allgaier N, Chaarani B, Garavan H, et al. Associations among Body Mass Index, Cortical Thickness, and Executive Function in Children. JAMA Pediatr. 2020;174(2):170–7. [PubMed: 31816020]
24. Ronan L, Alexander-Bloch A, Fletcher PC. Childhood obesity, cortical structure, and executive function in healthy children. Cereb Cortex [Internet]. 2020 Jul 19;30(4):2519–28. Available from: 10.1093/cercor/bhz257 [PubMed: 31646343]
25. Zhang Y, Ji W, Jiang F, Wu F, Li G, Hu Y, et al. Associations among body mass index, working memory performance, gray matter volume, and brain activation in healthy children. Cereb Cortex. 2023 May;33(10):6335–44. [PubMed: 36573454]
26. Hall PA, Best JR, Beaton EA, Sakib MN, Danckert J. Morphology of the prefrontal cortex predicts body composition in early adolescence: cognitive mediators and environmental moderators in the ABCD Study. Soc Cogn Affect Neurosci. 2023 Feb;18(1).
27. Jiang F, Li G, Ji W, Zhang Y, Wu F, Hu Y, et al. Obesity is associated with decreased gray matter volume in children: a longitudinal study. Cereb Cortex. 2023 Mar;33(7):3674–82. [PubMed: 35989308]
28. Alosco ML, Stanek KM, Galioto R, Korgaonkar MS, Grieve SM, Brickman AM, et al. Body mass index and brain structure in healthy children and adolescents. Int J Neurosci [Internet]. 2014 Jul 20;124(1):49–55. Available from: 10.3109/00207454.2013.817408 [PubMed: 23789910]
29. Silva CC V, Jaddoe VW V, Muetzel RL, Santos S, El Marroun H. Body fat, cardiovascular risk factors and brain structure in school-age children. Int J Obes (Lond). 2021 Nov;45(11):2425–31. [PubMed: 34267324]
30. Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, et al. A commonly carried allele of the obesity-related *FTO* gene is associated with reduced brain volume in the healthy elderly. Proc Natl Acad Sci U S A. 2010;107(18):8404–9. [PubMed: 20404173]
31. De Groot C, Felius A, Trompet S, De Craen AJM, Blauw GJ, Van Buchem MA, et al. Association of the fat mass and obesity-associated gene risk allele, rs9939609A, and reward-related brain structures. Obesity. 2015;23(10):2118–22. [PubMed: 26337140]
32. Rapuano KM, Zieselman AL, Kelley WM, Sargent JD, Heatherton TF, Gilbert-Diamond D. Genetic risk for obesity predicts nucleus accumbens size and responsivity to real-world food cues. Proc Natl Acad Sci [Internet]. 2017 Jan 3;114(1):160 LP – 165. Available from: http://www.pnas.org/content/114/1/160.abstract [PubMed: 27994159]

33. Wiemerslage L, Nilsson EK, Solstrand Dahlberg L, Ence-Eriksson F, Castillo S, Larsen AL, et al. An obesity-associated risk allele within the *FTO* gene affects human brain activity for areas important for emotion, impulse control and reward in response to food images. Eur J Neurosci. 2016 May;43(9):1173–80. [PubMed: 26797854]
34. Heni M, Kullmann S, Veit R, Ketterer C, Frank S, Machicao F, et al. Variation in the obesity risk gene *FTO* determines the postprandial cerebral processing of food stimuli in the prefrontal cortex. Mol Metab. 2014 Apr;3(2):109–13. [PubMed: 24634816]
35. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: Current knowledge and future directions. Obes Rev. 2012;13(1):43–56. [PubMed: 21902800]
36. Melka MG, Gillis J, Bernard M, Abrahamowicz M, Chakravarty MM, Leonard GT, et al. *FTO*, obesity and the adolescent brain. Hum Mol Genet. 2013 Mar;22(5):1050–8. [PubMed: 23201753]
37. Jansen E, Thapaliya G, Beauchemin J, D'Sa V, Deoni S, Carnell S. The Development of Appetite: Tracking and Age-Related Differences in Appetitive Traits in Childhood. Nutrients. 2023 Mar;15(6).
38. Bruchhage MMK, Ngo GC, Schneider N, D'Sa V, Deoni SCL. Functional connectivity correlates of infant and early childhood cognitive development. Brain Struct Funct [Internet]. 2020;225(2):669–81. Available from: 10.1007/s00429-020-02027-4 [PubMed: 32060640]
39. Avants BB, Tustison NJ, Stauffer M, Song G, Wu B, Gee JC. The Insight ToolKit image registration framework. Front Neuroinform [Internet]. 2014;8. Available from: 10.3389/fninf.2014.00044 [PubMed: 24600385]
40. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage. 2012 Aug;62(2):782–90. [PubMed: 21979382]
41. Bruchhage, Muriel M.K.Chen, Yaqing MH et al. Longitudinal Brain and Cognitive Development of the First 1000 Days: A Large Multi-CohortMulti-Scanner Study. Proc Intl Soc Mag Reson Med [Internet]. 2022; Available from: https://archive.ismrm.org/2022/0163.html
42. Sanchis-Segura C, Ibañez-Gual MV, Aguirre N, Cruz-Gómez ÁJ, Forn C. Effects of different intracranial volume correction methods on univariate sex differences in grey matter volume and multivariate sex prediction. Sci Rep. 2020 Jul;10(1):12953. [PubMed: 32737332]
43. Wang JL, Chiou JM, Müller HG. Functional Data Analysis. Annu Rev Stat Its Appl [Internet]. 2016 Jun 1;3(1):257–95. Available from: 10.1146/annurev-statistics-041715-033624
44. Chen K, Zhang X, Petersen A, Müller HG. Quantifying Infinite-Dimensional Data: Functional Data Analysis in Action. Stat Biosci. 2017;9(2):582–604.
45. Dai X, Hadjipantelis P, Wang JL, Deoni SC, Müller HG. Longitudinal associations between white matter maturation and cognitive development across early childhood. Hum Brain Mapp. 2019 Oct;40(14):4130–45. [PubMed: 31187920]
46. Chen Y, Dubey P, Müller HG, Bruchhage M, Wang JL, Deoni S. Modeling sparse longitudinal data in early neurodevelopment. Neuroimage [Internet]. 2021;237:118079. Available from: https://www.sciencedirect.com/science/article/pii/S1053811921003566 [PubMed: 34000395]
47. Bhattacharjee S, Chen Y, Zhu C, Chen H, Zhou Y, Gajardo Á, Müller HG. Package "fdaconcur". Available from: https://cran.r-project.org/web/packages/fdaconcur/index.html
48. Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, SK K. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. Cell Rep. 2014 Dec;249(6):2124–38.
49. Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. Neuron. 2016 Jan;89(2):248–68. [PubMed: 26796689]
50. Floresco SB. The nucleus accumbens: an interface between cognition, emotion, and action. Annu Rev Psychol. 2015 Jan;66:25–52. [PubMed: 25251489]
51. Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. Curr Opin Neurobiol. 2010 Apr;20(2):236–41. [PubMed: 20167473]
52. Rapuano KM, Tejavibulya L, Dinc EN, Li A, Davis H, Korn R, et al. Heightened sensitivity to high-calorie foods in children at risk for obesity: insights from behavior, neuroimaging, and genetics. Brain Imaging Behav. 2023 May;

53. Stice E, Yokum S, Voelker P. Relation of FTO to BOLD response to receipt and anticipated receipt of food and monetary reward, food images, and weight gain in healthy weight adolescents. Soc Cogn Affect Neurosci. 2020;15(10):1135–44. [PubMed: 31680145]

54. Khera A V, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, et al. Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. Cell [Internet]. 2019;177(3):587–596.e9. Available from: 10.1016/j.cell.2019.03.028 [PubMed: 31002795]

Study Important Questions

- What is already known about this subject?
  - Common obesity-associated genetic variants on *FTO* locus are associated with appetitive behaviors.
  - *FTO* variants have been associated with altered structure and function of frontostriatal brain regions in adults, adolescents and school-aged children.
- What are the new findings in your manuscript? Please remember to also include between the title page and structured abstract in your paper.
  - Children with two risk alleles on *FTO* SNP rs9939609 showed greater nucleus accumbens volume in the age interval of 750–2250 days (2–6y) than children with no risk alleles.
- How might your results change the direction of research or the focus of clinical practice? Please remember to also include between the title page and structured abstract in your paper.
  - Our results highlight the importance of investigating potentially dynamic relationships between genotype, brain, behavior, and weight throughout development.
  - Identifying effects of *FTO* on early developing appetite circuitry could inform on neurobehavioral mechanisms to target for early intervention.

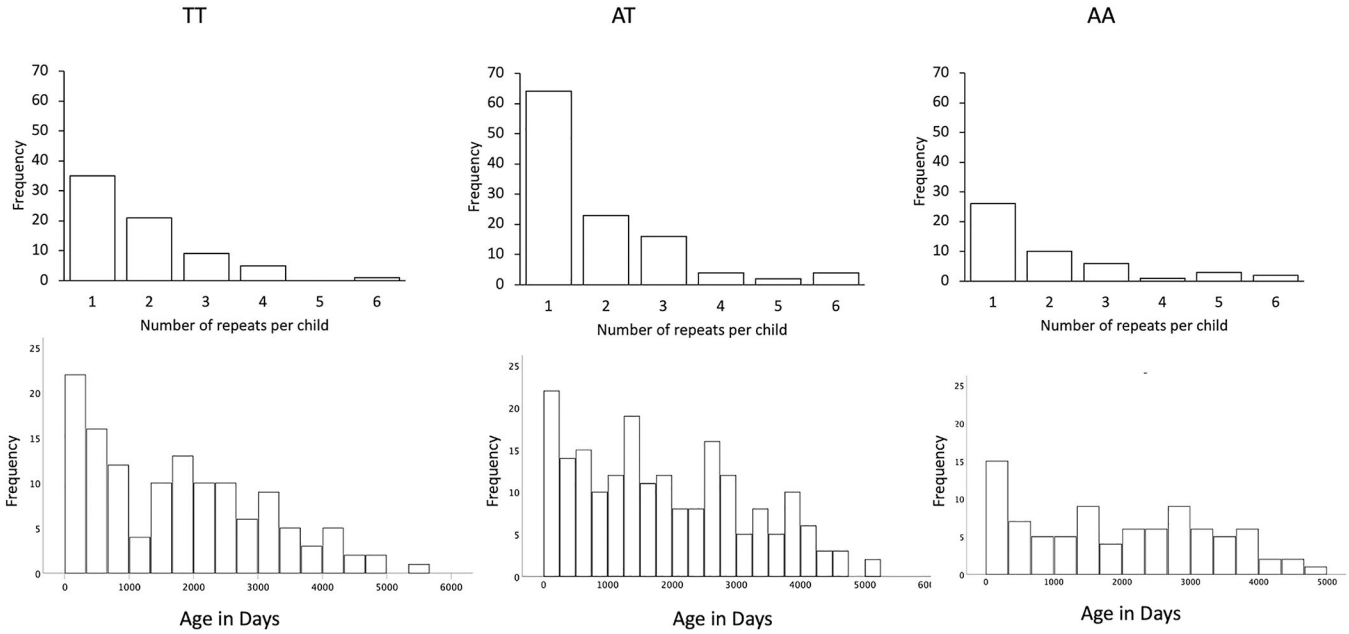

Figure 1.

Histograms portraying the number of repeat measurements per child (top) and ages (days) at assessment (bottom) by FTO genotype.

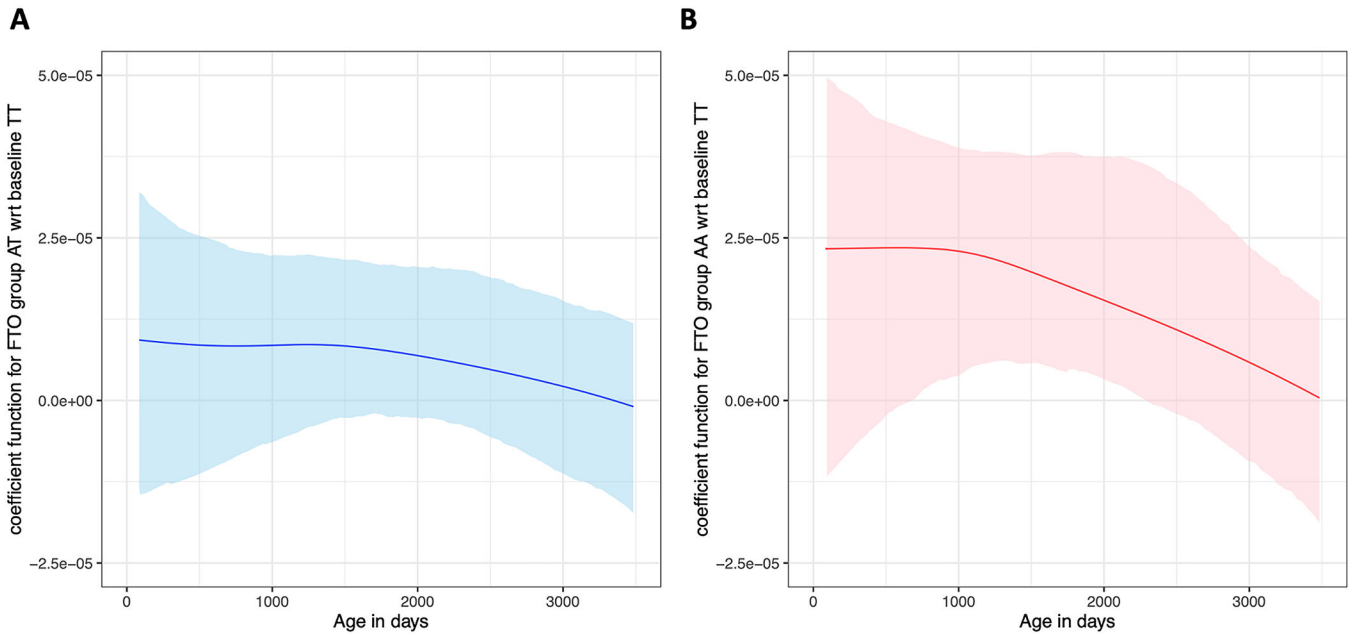

Figure 2.

A) The blue curve represents the estimated regression coefficient function of the FTO group AT on NAcc volume (as a fraction of global brain volume) growth trajectory with respect to the baseline group TT. The sky-blue band depicts the corresponding bootstrap pointwise 95% confidence interval. B) The red curve represents the estimated regression coefficient function of the FTO group AA on NAcc volume (as a fraction of glocal brain volume) growth trajectory with respect to the baseline group TT. The pink band illustrates the corresponding bootstrap pointwise 95% confidence interval.

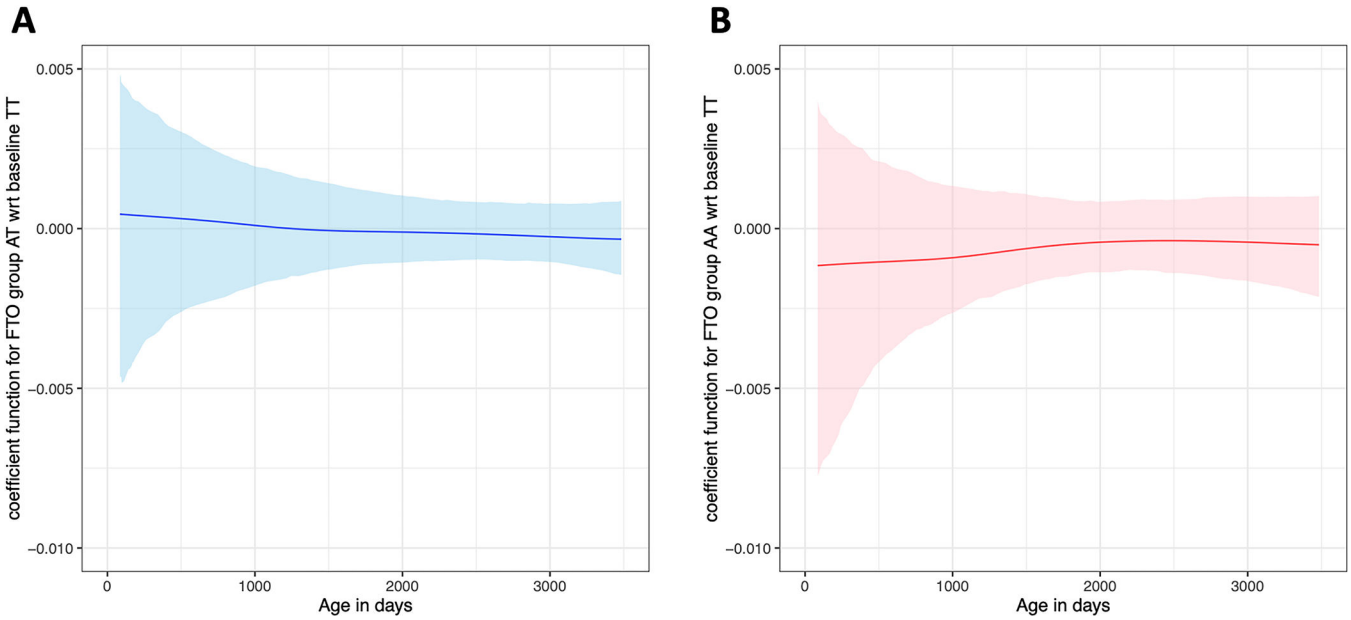

Figure 3.

A) The blue curve depicts the estimated regression coefficient function of the FTO group AT on the frontal lobe brain volume (as a fraction of global brain volume) growth trajectory with respect to the baseline group TT. The sky-blue band represents the corresponding bootstrap pointwise 95% confidence interval. B) The red curve represents the estimated regression coefficient function of the FTO group AA on frontal lobe brain volume (as a fraction of global brain volume) growth trajectory with respect to the baseline group TT (low obesity risk). The pink band illustrates the corresponding bootstrap pointwise 95% confidence interval.

Table 1:

Participant characteristics by *FTO* genotype

	Total (n=228)	TT(n=71)	AT (n=111)	AA (n=46)	*p-value*
Child sex					
Male (n)	126	45	59	22	
Female (n)	102	26	52	24	0.21
Child BMIz *	0.47 ± 1.29 (−2.23 – 4.76)	0.42 ± 1.24 (−2.23 – 3.95)	0.57 ± 1.35 (−2.14 – 4.76)	0.29 ± 1.24 (−1.49 – 4.28)	0.46
Child BMI category * n (%)					
Obesity	11 (4.8)	1 (1.4)	8 (7.2)	2 (4.3)	
Overweight	15 (6.5)	7 (9.9)	7 (6.3)	1 (2.2)	
At risk of overweight	43 (19.0)	13 (18.3)	22 (19.8)	8 (17.5)	
Not overweight	159 (69.7)	50 (70.4)	74 (66.7)	35 (76.0)	0.4
Maternal education n (%)					
University/College education (n)	144 (63.2)	44 (62.0)	69 (62.2)	31 (67.4)	
No university/college education (n)	84 (36.8)	27 (38.0)	42 (37.8)	15 (32.6)	0.80
Child race n (%)					
White	165 (72.4)	49 (69)	79 (71.2)	37 (80.4)	
Black or African American	16 (7.0)	4 (5.6)	10 (9.0)	2 (4.4)	
Mixed Race	21(9.2)	5 (7.1)	13 (11.7)	3 (6.5)	
Asian	13 (5.7)	10 (14.1)	3 (2.7)	0 (0)	
Other	13 (5.7)	3 (4.2)	6 (5.4)	4 (8.7)	0.05
Age of child at included timepoints (range in years)	5.09 ± 3.62 (0.2 – 15.0)	4.84 ± 3.68 (0.2 – 15.0)	5.16 ± 3.54 (0.2– 13.9)	5.30 ± 3.69 (0.2– 13.4)	0.60
Number of analysis timepoints per child	1.8 ± 1.2 (1 – 6)	1.8 ± 1.1 (1 – 6)	1.8 ± 1.2 (1 – 6)	1.9 ± 1.3 (1 – 6)	0.88

* BMIz values and BMI categories presented are with reference to WHO growth standards, based on data from each participant's last timepoint included in the analysis. Mean ± SD (range) reported