HHS Public Access

Author manuscript

Int J Obes (Lond). Author manuscript; available in PMC 2021 September 17.

Published in final edited form as:

Int J Obes (Lond). 2021 June ; 45(6): 1310–1320. doi:10.1038/s41366-021-00794-6.

Child Physical activity as a Modifier of the Relationship between Prenatal Exposure to Maternal Overweight/Obesity and Neurocognitive Outcomes in Offspring

Jasmin M. Alves, PhD[1,2], **Brendan C. Angelo, MS**[1,2], **Jennifer Zink, BA**[4], **Ting Chow, MPH**[3], **Alexandra G. Yunker, BA**[1,2], **Kristi Clark, PhD**[5], **Shan Luo, PhD**[1,2], **Britni Ryan Belcher, PhD**[4], **Megan M. Herting, PhD**[4], **Christina M. Dieli-Conwright, PhD**[6], **Anny H. Xiang, PhD**[3,&], **Kathleen A. Page, MD**[1,2,*,&]

[1]Division of Endocrinology, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089

[2]Diabetes and Obesity Research Institute, Keck School of Medicine, University of Southern California, Los Angeles CA 90089

[3]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA 91101

[4]Department of Preventive Medicine, University of Southern California, Los Angeles, CA 90032

[5]Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089

[6]Division of Population Sciences, Department of Medical Oncology, Dana-Farber Institute, Harvard Medical School, Boston, MA 02215

Abstract

Background/Objectives: With rising obesity rates among pregnant women, more children are exposed *in utero* to maternal obesity. In prior epidemiological studies, exposure to maternal obesity was associated with lower intelligence quotient (IQ) scores and worse cognitive abilities in offspring. Further studies have shown that offspring exposed to maternal obesity, exhibit differences in the white matter microstructure properties, fractional anisotropy (FA) and mean diffusivity (MD). In contrast, physical activity was shown to improve cognition and white matter microstructure during childhood. We examined if child physical activity levels modify the

*Correspondence can be made to Dr. Kathleen A. Page, MD, Associate Professor of Medicine, USC Keck School of Medicine, Division of Endocrinology, Diabetes and Obesity Research Institute, 2250 Alcazar Street; CSC 209, Los Angeles, CA 90089. kpage@usc.edu.

&Kathleen A. Page and Anny H. Xiang contributed equally and serve as joint senior authors.

Author Contributions: K.A.P. and A.H.X. had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis; K.A.P., S.L. and A.H.X. contributed to study concept and design; J.M.A., K.A.P. and A.H.X. drafted the manuscript; All authors critically revised the manuscript for intellectual content; Statistical and neuroimaging analyses were performed by J.M.A., B.C.A, J.Z., T.C., and A.H.X; M.M.H, and K.C. provided content knowledge and feedback for neuroimaging analyses; B.R.B and C.D.C provided content knowledge and feedback for physical activity and statistical methodology; K.A.P. and A.H.X. obtained funding; K.A.P. and A.H.X. provided study supervision.

Disclosure Summary: The authors have no conflicts of interest to disclose.

relationship between prenatal exposure to maternal obesity with IQ and white matter microstructure in offspring.

Subjects/Methods: One hundred children (59% girls) age 7–11 years underwent brain magnetic resonance imaging and IQ testing. Maternal pre-pregnancy BMI was abstracted from electronic medical records. White matter was assessed using diffusion tensor imaging with the measures, global FA, MD. The 3-day physical activity recall was used to measure moderate-to-vigorous physical activity and vigorous physical activity (VPA). Linear regression was used to test for interactions between prenatal exposure to maternal overweight/obesity and child PA levels on child IQ and global FA/MD.

Results: The relationship between prenatal exposure to maternal overweight/obesity and child IQ and global FA varied by child VPA levels. Children exposed to mothers with overweight/obesity who engaged in more VPA had higher IQ scores and global FA compared to exposed children who engaged in less VPA. Associations were independent of child age, sex, BMI Z-score and socioeconomic status. Children born to normal-weight mothers did not differ in either IQ or global FA by time in VPA.

Conclusions: Our findings support findings in rodent models and suggest that VPA during childhood modifies the relationship between prenatal exposure to maternal obesity and child IQ and white matter microstructure.

Keywords

Developmental Programming; Maternal Obesity; Physical Activity; White Matter; Intelligence

Introduction

The prevalence and severity of obesity during pregnancy continues to rise (1) posing significant health threats to both mothers and their children (2). Children exposed to maternal obesity *in utero* are at increased risk of developing metabolic disorders (3,4). Additionally, evidence suggests that exposure to maternal obesity negatively influences neurocognitive development in children (5–11), including lower intelligence quotient (IQ) scores, worse academic achievement scores, reduced hippocampal gray matter volume and reduced fractional anisotropy (FA); the latter of which is a commonly used metric for assessing white matter microstructure in the brain (5,7,8,10–12). Interventions mitigating the adverse effects of prenatal exposure to maternal obesity on child neurocognitive development have the potential to significantly impact public health.

Importantly, there are many factors that likely contribute to brain development and cognition in children (13–15). For example, both low socioeconomic status and child obesity have previously been associated with worse academic achievement scores and reductions in white matter microstructure integrity (13,15), whereas physical activity has been shown to provide cognitive benefits, such as higher IQ scores (16–23). Albeit, findings are mixed with some studies showing benefits of aerobic fitness but not moderate to vigorous physical activity (MVPA) on cognitive outcomes (24,25), and other studies showing no significant effects of in-school MVPA interventions on cognitive outcomes in children (26,27). Interestingly, randomized controlled trials specifically targeted at children with overweight/obesity have

shown that children who engaged in afterschool MVPA interventions had improved cognitive outcomes and differences in the brain white matter microstructure metrics, FA and mean diffusivity (MD), particularly in white matter tracts relevant to cognition such as the superior longitudinal fasciculus (17,20,28,29). Collectively, evidence suggests that PA may be particularly beneficial for vulnerable populations, such as children with overweight/obesity or children exposed to maternal obesity *in utero*. Similarly, promising results from studies in rodents have shown that engaging in PA rescues cognitive performance and hippocampal volume in offspring exposed to maternal obesity *in utero* (30); however, this has yet to be studied in humans.

Given prior evidence showing links between maternal obesity and poor neurocognitive outcomes in children as well as promising results in rodent models suggesting beneficial effects of physical activity on neurocognition in offspring exposed to maternal obesity, we aimed to examine if child PA levels have a modifying role on the association between prenatal exposure to maternal obesity and child IQ and white matter microstructure using a well-validated IQ assessment (31) and diffusion tensor imaging (DTI) (32), a sensitive neuroimaging approach for assessing white matter properties. We hypothesized that child PA would modify the relationship between prenatal exposure to maternal obesity and child IQ and white matter microstructure.

Methods

Participants

For this study, 137 children ages of 7 to 11 years old were recruited from Kaiser Permanente Southern California (KPSC) to participate in the BrainChild Study on the impact of intrauterine exposure to metabolic disorders on brain appetite pathways (Supplemental Information (SI) Figure 1) (5,33). KPSC is a large healthcare organization utilizing an integrated electronic medical record (EMR) system. Children were excluded if they were born to mothers diagnosed with diabetes before pregnancy or if the children had a history of neurological, psychiatric, metabolic or other significant medical disorders and/or use of medications known to alter metabolism or influence cognition. Children with contraindications to MRI were also excluded (left-handed, permanent metal-objects, claustrophobia). Each participating Institutional Review Board approved this study (University of Southern California (USC) # HS-14–00034 and KPSC # 10282). This study was in accordance with the Declaration of Helsinki. Participants' parents gave written informed consent and children provided written informed assent.

Exposure—Maternal pre-pregnancy BMI (kg/m^2) was calculated from maternal height (cm) and weight (kg) measurements closest to last menstrual period (LMP) from the EMR within 180 days before the last LMP or 90 days after the last LMP. Maternal height and weight measurements were collected during regular health visits and entered into the EMR by a healthcare provider. Maternal pre-pregnancy BMI was used as a marker for maternal obesity during pregnancy in accordance with previous literature (6,8,34). Mothers with pre-pregnancy BMI less than 25 kg/m^2 were classified as normal-weight. Mothers with pre-

pregnancy BMI equal to or greater than 25 kg/m^2 were classified as overweight/obesity consistent with Centers for Disease Control criteria (35).

In-person Visits—The study included two in-person visits, occurring on average 35 days apart. Visit 1 occurred at the USC Diabetes and Obesity Research Institute Clinical Research Unit. Children's height was measured by a trained staff member to the nearest 0.1 cm using a stadiometer (Seca 217 Portable Stadiometer Model PE-AIM-101, Perspective Enterprises, Portage MI USA) and weight to the nearest 0.1 kg using a calibrated digital scale (Tanita body composition analyzer SC-331S, Tanita Corporation, Chicago IL USA). BMI was calculated using the standard formula, weight (kg) divided by height (m^2). BMI z-scores and BMI percentiles (age and sex-specific standard deviation scores) were determined based on Center for Disease Control (CDC) standards (36). Participants were given the option of having their Tanner stage assessed by physical exam (37,38) and/or by a validated sex-specific assessment questionnaire (39). Fifty-one participants, (51%) opted for both physical exam and questionnaire. Forty-eight participants (48%) opted for self-reported puberty status only, and one participant (1%) participated only in the medical exam. The correlation between the physical exam and the questionnaire was 0.84. A self-reported 3-day physical activity recall (3DPAR) was also obtained (40,41). Visit 2 occurred at USC Dana and David Dornsife Neuroimaging Center and included cognitive measures, brain magnetic resonance imaging (MRI), and another height and weight measurement. Height and weight measurements were averaged from the two study visits to calculate BMI z-scores and BMI percentiles.

Physical Activity Assessment—Physical activity was assessed using the 3DPAR (40,42). The 3DPAR has previously been used in pediatric studies and validated with objective measures of physical activity using accelerometer devices (40,43–45). For approximately 30 minutes during visit 1, a trained staff asked participants, with their parents' input, to recall their activities from 7:00am to 12:00am in 30-minute increments for the previous three days. Activities were recorded and classified based on the activity most similar on a 73-item reference sheet. The participant with the help of their parent was then asked to rate the intensity of each activity, ranging from light, moderate, hard, to very hard. Self-reported activities were then categorized as either light physical activity (LPA), MVPA, or vigorous physical activity (VPA) based on corresponding metabolic equivalent (MET) values from the Compendium of Physical Activities (40,42). Activities with METs ≥1.6 and <3 were classified as LPA, METs ≥ 3 were classified as MVPA and METs ≥ 6 were classified as VPA. An example of LPA includes playing an instrument. MVPA includes activities like walking the dog, and an example of VPA is playing soccer. The number of 30-minute increments spent in either LPA, MVPA, or VPA each day was summed and converted to minutes and then divided by 3, and the final output was the average time spent in LPA, MVPA, or VPA per day (40,41).

General Cognitive Function—The shortened 2nd edition of the Wechsler Abbreviate Scale for Intelligence for children (WASI-II) was used to assess IQ (31). The WASI-II is a well-established IQ assessment and is validated for ages 6 to 90 (31). The standardized norm is 100 with a standard deviation of 15. Two parts of the WASI-II were administered,

vocabulary and matrix reasoning, to determine a composite IQ score. Raw scores from the vocabulary and matrix reasoning portion were converted to age-adjusted T-scores. The sum of the T-scores were then converted to a composite IQ score.

MRI Methods—During the second visit, after a mock scanner training session, a brain MRI was performed using a Siemens MAGNETOM Prisma^{fit} 3T MRI scanner (Siemens Medical Systems, Erlangen Germany) with a 20-channel phased array coil. The MRI session started with a localizer scan. A 9 minutes, 29 second diffusion weighted image (DWI) was acquired using a dual spin echo, single shot, pulsed gradient, echo planar imaging sequence in 64 diffusion sensitized gradient directions with the following parameters: TR=8 100 ms; TE=69 ms; flip angle=90°; 70 axial slices; 2 × 2 × 2-mm^3 voxel size; FOV=256 mm; *b* value=1 000s/mm^2, with one *b0* collected at the beginning of the scan. Additional imaging sequences were also performed as a part of a larger study, and a subset of the participants have been included in other publications (5,33). A T2-weighted image was also assessed by a trained neuroradiologist to check for brain abnormalities.

Using FSL (FMRIB Software Library, v6.0) (46), DWI's were preprocessed, which included skull-stripping using the brain extraction tool (BET) (47) and correction for motion and eddy current artifacts using the eddy_correct module (46). DWI's were then fitted to create FA and MD images using the Quantitative Imaging Toolkit (48). Mean FA/MD for each subject was then extracted to compare global FA/MD across subjects exposed to varying levels of maternal obesity and varying time in LPA, MVPA and VPA. Tract-based spatial statistics (TBSS, v1.2) (49), a part of FSL, was then used to complete a whole brain voxel-based approach comparing how maternal pre-pregnancy BMI and time spent in PA was related to clusters in white matter tracts, using FA and MD metrics. FA images were first aligned to a common space and a target image was selected using FNIRT(50) and then averaged and a threshold of >0.2 was used to make a skeleton mask of white matter tracts common to all participants. Lastly, each subject's FA image was projected onto the skeletonized mask to perform group-level statistics using FSL's randomise tool (51).

Statistical Analysis—Participant descriptive statistics, including means and frequencies, were assessed. Time spent in LPA, MVPA, and VPA were not normally distributed, a square-root transformation was applied to normalize the distribution prior to the regression analysis when treated as continuous variables. Multiple linear regression was used to analyze relationships between maternal pre-pregnancy BMI and time spent in LPA/MVPA/VPA, both as continuous variables and categorical variables, with child IQ and global FA/MD as the outcome variables. An interaction term between maternal pre-pregnancy BMI and child LPA/MVPA/VPA levels were included to test whether child PA levels modify the relationship between prenatal exposure to maternal obesity and child IQ scores and brain outcomes. A priori covariates previously shown to influence neurocognition were included in each regression analysis, including child age in years (52), sex (14,53), socioeconomic status (SES) (13), assessed using household income at birth, estimated based on census tract of residence and expressed as a continuous variable, and maternal education at birth, extracted from birth certificates in the EMR as a categorical variable with the following categories: "high-school or some high-school", "some college" and "college and post-

education", and BMI z-score (15). For interpretative purposes, children's VPA was categorized either as above the median reported time spent in VPA for the sample, or below the median reported time spent in VPA; maternal pre-pregnancy BMI was categorized as mothers with normal-weight (BMI<25) or overweight/obesity (BMI≥25).

For the whole brain analysis, FSL's randomise tool (51), based on general linear models, was used to identify whether clusters of voxels of FA/MD are associated with child PA level and/or maternal pre-pregnancy BMI and interaction between the two. The design matrix used child age and sex as covariates since these covariates were shown to have age-related increases of FA and significantly greater clusters of FA in girls compared to boys. The threshold-free cluster enhancement option with 5000 permutations (54) was utilized to identify significant clusters using family wise error rate (FWER) with a threshold of $p<0.05$. The Johns Hopkins University white matter tractography atlas was then used to identify the location of significant clusters (55).

Of the 100 children included in analyses, 91% of the children were prepubertal and Tanner stage of puberty was not associated with outcome variables, IQ ($r=-0.046$, $p=0.65$), global FA ($r=0.005$, $p=0.96$), or global MD ($r=-0.076$, $p=0.45$), or with any voxels of FA, therefore, Tanner Stage was not included as a covariate in final models. P-values < 0.05 were interpreted as statistically significant. SAS 9.4 statistical software (SAS Institute, Cary, NC USA) was used for all statistical analyses.

Results

Of the 137 children enrolled into the study, 100 children completed all of the testing (i.e., MRI, IQ testing, and 3DPAR) (SI Figure 1). The demographics of participants who completed all of the testing did not differ from participants who did not (SI Table 1). For children who completed all of the testing, the mean ± SD age was 8.51 ± 1.00 years old, 91% of the children were pre-pubertal (Tanner Stage <2), and 59% were girls (Table 1). The median reported time spent in LPA per day was 60 minutes, MVPA per day was 100 minutes and VPA per day was 10 minutes. Mean ± SD child IQ scores were 108.80 ± 13.74, which is less than one SD higher than a nationally representative sample (31). Mean ± SD maternal pre-pregnancy BMI was 30.08 ± 7.11 and 41% of mothers had obesity. Other child and maternal characteristics can be found in Table 1. Children exposed to mothers with overweight/obesity did not differ from children exposed to mothers with normal-weight in mean age, Tanner Stage, sex, LPA, MVPA, VPA, IQ, or global FA, but had significantly greater BMI z-scores, a greater frequency of children with obesity, and had lower family incomes (SI Table 2). Additionally, a scatterplot of child VPA in minutes per day stratified by maternal weight status (normal-weight vs overweight/obesity) can be found in SI Figure 2.

For the outcome of child IQ score, in the model without considering PA levels, maternal pre-pregnancy BMI was negatively associated with child IQ scores ($\beta = -0.31$; 95% CI, −0.67 to 0.06; $p=0.10$) and the association remained after adjusting for child's age, sex, and SES, and BMI z-score ($\beta = -0.38$; 95% CI, −0.79 to 0.03; $p=0.07$) although the association did not reach statistical significance (Table 2). For the outcome of global FA, maternal pre-

pregnancy BMI was not significantly associated with global FA. Using TBSS as a whole brain approach, there were also no significant voxels of FA or MD associated with maternal pre-pregnancy BMI.

When physical activity levels were included in the model as a main effect without considering the interaction with maternal pre-pregnancy BMI, greater reported time spent in VPA was associated with higher child IQ scores and greater global FA in both unadjusted and adjusted models and after further adjusting for pre-pregnancy BMI (Table 2; Figure 1). Compared to children who reported below the median time in VPA, children who reported above the median of time in VPA also had significant clusters of FA voxels in the white matter skeleton that corresponds to the left and right superior longitudinal fasciculus (SLF) and right anterior thalamic radiation (ATR), after controlling for maternal pre-pregnancy BMI, child age and sex (Figure 2; SI Table 3). These clusters remained significant at the FWER threshold of $p<0.05$. There were no significant clusters of MD associated with VPA. Time spent in MVPA was associated with child IQ scores after adjusting for covariates but was not associated with global FA or MD (Table 2). TBSS revealed no significant clusters of FA or MD voxels associated with MVPA. Time spent in LPA was not associated with child IQ scores and global FA or MD before or after adjusting for covariates (Table 2) and was also not associated with clusters of FA or MD.

However, when testing for an interaction between maternal obesity and physical activity levels in the model, we observed a significant interaction between maternal obesity status and time spent in VPA on child IQ scores ($p=0.01$ testing for interaction, Figure 3A) and on global FA ($p=0.01$ testing for interaction, Figure 3B). When data were stratified by maternal obesity status, among 76 children whose mothers were overweight/obese at the time of pregnancy, the 38 children who reported above the median time spent in VPA had significantly higher IQ scores (age, sex, SES and BMI z-score adjusted $\beta=8.44$; 95% CI, 1.43 to 15.46; $p=0.02$) and greater global FA (adjusted $\beta=0.008$; 95% CI, 0.002 to 0.014; $p=0.007$) compared to the 38 children who reported below the median time spent in VPA (Table 3). Among 24 children whose mothers were of a normal-weight at the time of pregnancy, those (n=15) who reported above the median of 10 minutes in VPA had higher IQ scores than those (n=9) who reported less than 10 minutes, but the difference was not statistically significant ($\beta=5.76$; 95% CI, −4.52 to 16.03; $p=0.29$, Table 3), and there was no difference in global FA between high vs low PA levels (Table 3).

We also observed a significant interaction using a whole brain approach to identify clusters of FA. Our initial significance threshold revealed an interaction between pre-pregnancy BMI category and VPA levels that covered the majority of the white matter skeleton (SI Table 4). In order to get a more precise location of significant clusters, we increased the significance threshold to $p<0.01$ and found clusters remained in the left forceps major, left ATR, right cingulate gyrus, right inferior frontal occipital fasciculus (IFOF), and cingulum (hippocampal portion) where children exposed to maternal overweight/obesity who were above the median VPA had higher FA values as compared to those that reported lower VPA levels (SI Table 5). No significant interactions were found between maternal obesity status and time spent in MVPA or LPA on child's outcomes ($p>0.27$ for all interaction tests).

Discussion

Engaging in physical activity has been shown to have beneficial effects on child cognition and brain development (16–19,21,22,28,56). Because prenatal exposure to mothers with obesity has been shown to negatively impact child neurocognition (5,7,8), we examined if engaging in physical activity could be a potential approach to ameliorate the adverse neurocognitive consequences of prenatal exposure to mothers with obesity.

Our data support prior findings in animal models (30) and suggest that engaging in physical activity during childhood may have the potential to modify the relationship between prenatal exposure to maternal obesity and child neurocognition, and thus offers a promising approach to mitigate the adverse effects associated with prenatal exposure to maternal obesity on child neurocognition. We found significant interactions between prenatal exposure to maternal obesity and child VPA levels on both child IQ scores and global FA. In stratified analyses we found that children exposed to mothers with overweight/obesity who engaged in at least 10 minutes per day in VPA had higher IQ scores and greater global FA compared to children exposed to mothers with overweight/obesity who engaged in less than 10 minutes per day in VPA. Children born to normal-weight mothers did not differ in either IQ or global FA by time spent in VPA. These findings suggest that physical activity is associated with improved neurocognition during childhood and may be particularly beneficial for children exposed to mothers with overweight/obesity.

In agreement with other studies in children, we found that children who were more physically active had higher IQ scores and greater global FA (22,23,57,58). We additionally observed that these associations were independent of prenatal exposure to mothers with obesity. Moreover, we observed that children who reported spending at least 10 minutes per day in VPA had greater FA in specific clusters within the left and right SLF and right ATR, independent of prenatal exposure to mothers with obesity. Prior pediatric studies have shown that physical activity interventions contribute to greater FA in the SLF, a white matter tract implicated in many aspects of cognition, including attention, IQ, and language abilities (29). Together with prior reports, these findings support positive associations of physical activity with SLF white matter microstructure during childhood.

In contrast to FA, we did not observe differences in MD in children who reported above compared to below the median VPA. FA is a composite DTI measure corresponding to the extent of uniform directionality of white matter tracts, and higher FA values suggest increased fiber bundle density and/or increased myelination (59–61). MD is the average rate of water diffusion independent of direction, and compromises two components, radial diffusivity (RD) and axial diffusivity (AD) (61,62). RD is an indirect measure of decreases in myelination, and AD is an indirect measure of axonal pruning (62). In line with our findings, Chaddock et al. showed that more physically fit children had increased FA but no differences in AD in the Superior Longitudinal Fasciculus (63). While a number of studies have shown that physical activity is positively associated with FA in several white matter tracts (28,56,63), a few cross-sectional studies (58,64) have shown that physical activity or cardiorespiratory fitness are negatively associated with MD in various white matter tracts, which we did not observe in our cohort of 7–11 year old children and could be related to

age-dependent differences in brain maturation. Recent evidence demonstrates significant developmental changes in microstructural properties, including increases in FA and decreases in MD, that occur during childhood and adolescence (60), and highlight the importance of longitudinal studies to further characterize the effects of physical activity on brain development during childhood and adolescence.

A wealth of data demonstrates the efficacy of physical activity interventions for improving cognition across the lifespan and strengthening white matter pathways particularly during childhood (16–18,21,22,28,56,65). Potential mechanisms by which physical activity improves cognition include increasing levels of the neurotrophin, brain-derived neurotrophic factor (BDNF), and increasing neurogenesis in the hippocampus (65–67), a brain region important for many aspects of learning and memory, and through strengthening the SLF and/or corpus callosum white matter pathways (28,56). Additionally, physical activity may also benefit cognition through indirect pathways, such as the secretion of myokines that affect neural growth factors and/or increases in insulin sensitivity (68,69). Animal studies have shown that improvements in peripheral insulin sensitivity from exercise contribute to improved insulin signaling in the brain and in turn, enhanced cognition (68,69). Correspondingly, prior studies have shown that *in utero* exposure to maternal obesity impacts offspring insulin sensitivity (4,70). Therefore, future studies should consider assessing insulin sensitivity as a potential mediating factor in the association between prenatal exposure to maternal obesity and offspring neurocognitive outcomes.

Interestingly, prior studies in humans showed that physical activity contributes to whole-body insulin sensitivity (71–73) and improved neurocognition (66) in a dose-dependent manner with VPA having larger effects. Our results are among the first to suggest that physical activity intensity is also related to improved neurocognition during childhood. The majority of studies in children have assessed MVPA rather than VPA, specifically (18,56,58). Future studies are needed to determine the type of physical activities, the precise duration, and the optimal intensity of physical activity ranging from light, moderate to vigorous, that is *most* beneficial for neurocognition during childhood. These findings could be particularly important for children at risk of cognitive impairments, such as children exposed *in utero* to mothers with obesity.

Limitations

Our study design had many strengths; however, there were some limitations. While we used a well-validated assessment for IQ and an objective measure of maternal pre-pregnancy BMI from EMR, we used a self-report for assessing physical activity, rather than an objective measure, such as an accelerometer. Although self-reports are subject to recall bias, children in our cohort reported spending a similar time engaged in VPA to elementary-aged children in the National Health and Nutritional Examination Survey (NHANES) dataset (74). One of the advantages of using self-reported activities over accelerometers in children is that accelerometers may exclude time spent in team sports or water activities due to logistical reasons, whereas these vigorous physical activities can be captured by self-report and could be used to plan intervention studies. Additionally, we did not collect IQ assessments of the mothers and therefore were unable to control for maternal IQ as a covariate. Future studies

should consider collecting IQ assessments on both the mother and the child. Our modest sample size may limit the generalizability of the results, and future studies with a larger sample size are needed to confirm whether physical activity mitigates the association between prenatal exposure to maternal obesity and worse neurocognitive outcomes in children. Lastly, due to the retrospective design of our study, there may have been other factors that were not accounted for that could have contributed to the associations observed here such as child diet. Importantly, a randomized controlled study is needed to test whether PA ameliorates the neurocognitive consequences of prenatal exposure to maternal obesity.

Conclusions

We found that engaging in VPA during childhood modified the relationship between prenatal exposure to maternal obesity and child IQ scores and white matter microstructure. Children exposed to mothers with overweight/obesity who engaged in more VPA had higher IQ scores and greater global FA; whereas these associations were not present in children exposed to mothers with normal-weight during pregnancy. We also found that time spent in VPA was associated with higher IQ scores and greater global FA, independent of prenatal exposure to mothers with obesity. These findings suggest that engaging in VPA during childhood may be a promising strategy to ameliorate the adverse consequences of prenatal exposure to maternal obesity on child neurocognition. Future intervention studies are necessary to test this possibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The authors would like to thank the families who participate in the BrainChild Study. The authors would also like to thank Ana Romero for managing the BrainChild study, Alexis Defendis for study assistance, Mayra Martinez and Janet Mora-Marquez for recruiting volunteers, the staff at Dana and David Dornsife Cognitive Neuroimaging Center at USC and the staff at the USC Diabetes and Obesity Research Institute.

Funding sources: This work was supported by an American Diabetes Association Pathway Accelerator Award (#1-14-ACE-36) (PI: K.A.P) and in part by the National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) R01DK116858 (PIs: K.A.P, A.H.X) and the National Institute Of Mental Health of the National Institutes of Health under Award Number F31MH115640 (PI: J.M.A). A Research Electronic Data Capture, REDCap, database was used for this study, which is supported by the Southern California Clinical and Translational Science Institute (SC CTSI) through NIH UL1TR001855.

Data availability:

The datasets generated during and analyzed during the current study are available from the corresponding author (K.A.P.), on reasonable request.

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014 2 26;311(8):806–14. [PubMed: 24570244]
2. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007–2008 to 2015–2016. JAMA. 2018 4 24;319(16):1723. [PubMed: 29570750]

3. Bider-Canfield Z, Martinez MP, Wang X, Yu W, Bautista MP, Brookey J, et al. Maternal obesity, gestational diabetes, breastfeeding and childhood overweight at age 2 years: Maternal exposures and childhood overweight. Pediatr Obes. 2017 4;12(2):171–8. [PubMed: 26956226]

4. Mingrone G, Manco M, Mora MEV, Guidone C, Iaconelli A, Gniuli D, et al. Influence of Maternal Obesity on Insulin Sensitivity and Secretion in Offspring. Diabetes Care. 2008 9 1;31(9):1872–6. [PubMed: 18535193]

5. Alves JM, Luo S, Chow T, Herting M, Xiang AH, Page KA. Sex differences in the association between prenatal exposure to maternal obesity and hippocampal volume in children. Brain Behav. 2020 1 5;e01522. [PubMed: 31903710]

6. Basatemur E, Gardiner J, Williams C, Melhuish E, Barnes J, Sutcliffe A. Maternal Prepregnancy BMI and Child Cognition: A Longitudinal Cohort Study. PEDIATRICS. 2013 1 1;131(1):56–63. [PubMed: 23230067]

7. Casas M, Chatzi L, Carsin A-E, Amiano P, Guxens M, Kogevinas M, et al. Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. Int J Epidemiol. 2013 4;42(2):506–17. [PubMed: 23569191]

8. Huang L, Yu X, Keim S, Li L, Zhang L, Zhang J. Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project. Int J Epidemiol. 2014 6;43(3):783–92. [PubMed: 24569381]

9. Neggers YH, Goldenberg RL, Ramey SL, Cliver SP. Maternal prepregnancy body mass index and psychomotor development in children. Acta Obstet Gynecol Scand. 2003 3;82(3):235–40. [PubMed: 12694119]

10. Tanda R, Salsberry PJ, Reagan PB, Fang MZ. The impact of prepregnancy obesity on children's cognitive test scores. Matern Child Health J. 2013 2;17(2):222–9. [PubMed: 22350633]

11. Widen EM, Kahn LG, Cirillo P, Cohn B, Kezios KL, Factor-Litvak P. Prepregnancy overweight and obesity are associated with impaired child neurodevelopment. Matern Child Nutr. 1;14(1):e12481.

12. Ou X, Thakali KM, Shankar K, Andres A, Badger TM. Maternal adiposity negatively influences infant brain white matter development. Obes Silver Spring Md. 2015 5;23(5):1047–54.

13. Rosen ML, Sheridan MA, Sambrook KA, Meltzoff AN, McLaughlin KA. Socioeconomic disparities in academic achievement: A multi-modal investigation of neural mechanisms in children and adolescents. NeuroImage. 2018 6;173:298–310. [PubMed: 29486324]

14. Arden R, Plomin R. Sex differences in variance of intelligence across childhood. Personal Individ Differ. 2006 7 1;41(1):39–48.

15. Yau PL, Kang EH, Javier DC, Convit A. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity: Brain Alterations in Adolescent Obesity. Obesity. 2014 8;22(8):1865–71. [PubMed: 24891029]

16. Bunketorp Käll L, Malmgren H, Olsson E, Lindén T, Nilsson M. Effects of a Curricular Physical Activity Intervention on Children's School Performance, Wellness, and Brain Development. J Sch Health. 2015 10;85(10):704–13. [PubMed: 26331753]

17. Davis CL, Tomporowski PD, McDowell JE, Austin BP, Miller PH, Yanasak NE, et al. Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol Off J Div Health Psychol Am Psychol Assoc. 2011 1;30(1):91–8.

18. Have M, Nielsen JH, Ernst MT, Gejl AK, Fredens K, Grøntved A, et al. Classroom-based physical activity improves children's math achievement – A randomized controlled trial. PLOS ONE. 2018 12 17;13(12):e0208787. [PubMed: 30557397]

19. Huang T, Tarp J, Domazet SL, Thorsen AK, Froberg K, Andersen LB, et al. Associations of Adiposity and Aerobic Fitness with Executive Function and Math Performance in Danish Adolescents. J Pediatr. 2015 10;167(4):810–5. [PubMed: 26256018]

20. Raine LB, Khan NA, Drollette ES, Pontifex MB, Kramer AF, Hillman CH. Obesity, Visceral Adipose Tissue, and Cognitive Function in Childhood. J Pediatr. 2017 8;187:134–140.e3. [PubMed: 28622956]

21. Reed JA, Einstein G, Hahn E, Hooker SP, Gross VP, Kravitz J. Examining the impact of integrating physical activity on fluid intelligence and academic performance in an elementary school setting: a preliminary investigation. J Phys Act Health. 2010 5;7(3):343–51. [PubMed: 20551490]
22. Makharia A, Nagarajan A, Mishra A, Peddisetty S, Chahal D, Singh Y. Effect of environmental factors on intelligence quotient of children. Ind Psychiatry J. 2016;25(2):189–94. [PubMed: 28659699]
23. El-Kholy T, Elsayed E. Association of physical activity and health status with intelligence quotient of high school students in Jeddah. J Phys Ther Sci. 2015 7;27(7):2039–43. [PubMed: 26311922]
24. Pindus DM, Drollette ES, Scudder MR, Khan NA, Raine LB, Sherar LB, et al. Moderate-to-Vigorous Physical Activity, Indices of Cognitive Control, and Academic Achievement in Preadolescents. J Pediatr. 2016 6 1;173:136–42. [PubMed: 26973149]
25. Pindus DM, Davis RDM, Hillman CH, Bandelow S, Hogervorst E, Biddle SJH, et al. The relationship of moderate-to-vigorous physical activity to cognitive processing in adolescents: findings from the ALSPAC birth cohort. Psychol Res. 2015 9;79(5):715–28. [PubMed: 25351943]
26. Donnelly JE, Hillman CH, Greene JL, Hansen DM, Gibson CA, Sullivan DK, et al. Physical activity and academic achievement across the curriculum: Results from a 3-year cluster-randomized trial. Prev Med. 2017 6;99:140–5. [PubMed: 28193490]
27. Konijnenberg C, Fredriksen PM. The effects of a school-based physical activity intervention programme on children's executive control: The Health Oriented Pedagogical Project (HOPP). Scand J Public Health. 2018 5;46(21_suppl):82–91. [PubMed: 29754580]
28. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al. Improved Frontoparietal White Matter Integrity in Overweight Children Is Associated with Attendance at an After-School Exercise Program. Dev Neurosci. 2014;36(1):1–9. [PubMed: 24457421]
29. Urger SE, De Bellis MD, Hooper SR, Woolley DP, Chen SD, Provenzale J. The Superior Longitudinal Fasciculus in Typically Developing Children and Adolescents: Diffusion Tensor Imaging and Neuropsychological Correlates. J Child Neurol. 2015 1 1;30(1):9–20. [PubMed: 24556549]
30. Kim T-W, Park H-S. Physical exercise improves cognitive function by enhancing hippocampal neurogenesis and inhibiting apoptosis in male offspring born to obese mother. Behav Brain Res. 2018 7;347:360–7. [PubMed: 29551732]
31. Irby SM, Floyd RG. Test Review: Wechsler Abbreviated Scale of Intelligence, Second EditionWechslerD.Wechsler Abbreviated Scale of Intelligence, Second Edition. 2011; San Antonio, TX: Pearson. Can J Sch Psychol. 2013 9;28(3):295–9.
32. Tamnes CK, Roalf DR, Goddings A-L, Lebel C. Diffusion MRI of white matter microstructure development in childhood and adolescence: Methods, challenges and progress. Dev Cogn Neurosci. 2018 10 1;33:161–75. [PubMed: 29229299]
33. Page KA, Luo S, Wang X, Chow T, Alves J, Buchanan TA, et al. Children Exposed to Maternal Obesity or Gestational Diabetes Mellitus During Early Fetal Development Have Hypothalamic Alterations That Predict Future Weight Gain. Diabetes Care. 2019 8;42(8):1473–80. [PubMed: 31332028]
34. Han E, Abrams B, Sridhar S, Xu F, Hedderson M. Validity of Self-Reported Pre-Pregnancy Weight and Body Mass Index Classification in an Integrated Health Care Delivery System. Paediatr Perinat Epidemiol. 2016;30(4):314–9. [PubMed: 26961120]
35. CDC. Defining Adult Overweight and Obesity | Overweight & Obesity. Available from: https://www.cdc.gov/obesity/adult/defining.html [Accessed 10 January 2018].
36. CDC. About Child & Teen BMI | Healthy Weight. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html [Accessed 27 November 2018].
37. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291–303. [PubMed: 5785179]
38. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13–23. [PubMed: 5440182]
39. Rasmussen AR, Wohlfahrt-Veje C, Tefre De Renzy-Martin K, Hagen CP, Tinggaard J, Mouritsen A, et al. Validity of Self-Assessment of Pubertal Maturation. PEDIATRICS. 2015;135(1).

40. Pate RR, Ross R, Dowda M, Trost SG, Sirard JR. Validation of a 3-Day Physical Activity Recall Instrument in Female Youth. Pediatr Exerc Sci. 2003 8 20;15(3):257–65.
41. Hearst M, Sirard J, Lytle L, Dengel D, Berrigan D. Comparison of three measures of physical activity and associations with blood pressure, HDL and body composition in a sample of adolescents. J Phys Act Health. 2012 1;9(1):78–85. [PubMed: 22232509]
42. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 compendium of physical activities: A second update of codes and MET values. Vol. 43, Medicine and Science in Sports and Exercise. 2011. p. 1575–81. [PubMed: 21681120]
43. Powell KE, Roberts AM, Ross JG, Phillips MAC, Ujamaa DA, Zhou M. Low Physical Fitness Among Fifth- and Seventh-Grade Students, Georgia, 2006. Am J Prev Med. 2009 4 1;36(4):304–10. [PubMed: 19201145]
44. Dollman J, Stanley R, Wilson A. The Concurrent Validity of the 3-Day Physical Activity Recall in Australian Youth. Pediatr Exerc Sci. 2015 5;27(2):262–7. [PubMed: 25902553]
45. Pavlidou S, Michalopoulou M, Aggelousis N, Taxildaris K, Bounova A. Convergent Validity and Reliability of a Three-Day Physical Activity Record in Greek Children 2010;8.
46. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage. 2004 1 1;23:S208–19. [PubMed: 15501092]
47. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002 11;17(3):143–55. [PubMed: 12391568]
48. Cabeen RP, Laidlaw DH, Toga AW. Quantitative Imaging Toolkit: Software for Interactive 3D Visualization, Processing, and Analysis of Neuroimaging Datasets. In: Proc Intl Soc Mag Reson Med. 2018.
49. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006;31(4):1487–1505. [PubMed: 16624579]
50. Andersson JL, Jenkinson M, and Smith S. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. FMRIB Anal Group Univ Oxf. Available from: https://www.fmrib.ox.ac.uk/datasets/techrep/tr07ja2/tr07ja2.pdf [Accessed 14 May 2015].
51. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. NeuroImage. 2014 5 15;92:381–97. [PubMed: 24530839]
52. Dimond D, Rohr CS, Smith RE, Dhollander T, Cho I, Lebel C, et al. Early childhood development of white matter fiber density and morphology. NeuroImage. 2020 4 15;210:116552. [PubMed: 31972280]
53. Wang Y, Adamson C, Yuan W, Altaye M, Rajagopal A, Byars AW, et al. Sex differences in white matter development during adolescence: A DTI study. Brain Res. 2012 10 10;1478:1–15. [PubMed: 22954903]
54. Smith SM, Nichols TE. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage. 2009 1 1;44(1):83–98. [PubMed: 18501637]
55. Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, et al. Tract Probability Maps in Stereotaxic Spaces: Analyses of White Matter Anatomy and Tract-Specific Quantification. NeuroImage. 2008 1 1;39(1):336–47. [PubMed: 17931890]
56. Chaddock-Heyman L, Erickson KI, Kienzler C, Drollette ES, Raine LB, Kao S-C, et al. Physical Activity Increases White Matter Microstructure in Children. Front Neurosci. 2018 12 19;12:950. [PubMed: 30618578]
57. Rodriguez-Ayllon M, Cornejo IE, Verdejo-Román J, Muetzel RL, Migueles JH, Mora-Gonzalez J, et al. Physical Activity, Sedentary Behavior, and White Matter Microstructure in Children with Overweight or Obesity. Med Sci Sports Exerc. 2019 12 23;
58. Rodriguez-Ayllon M, Derks IPM, van den Dries MA, Esteban-Cornejo I, Labrecque JA, Yang-Huang J, et al. Associations of physical activity and screen time with white matter microstructure in children from the general population. NeuroImage. 2020 1 15;205:116258. [PubMed: 31605827]

59. Snook L, Paulson L-A, Roy D, Phillips L, Beaulieu C. Diffusion tensor imaging of neurodevelopment in children and young adults. NeuroImage. 2005 7 15;26(4):1164–73. [PubMed: 15961051]
60. Bava S, Thayer R, Jacobus J, Ward M, Jernigan TL, Tapert SF. Longitudinal characterization of white matter maturation during adolescence. Brain Res. 2010 4 23;1327:38–46. [PubMed: 20206151]
61. Bockhorst KH, Narayana PA, Liu R, Ahobila-Vijjula P, Ramu J, Kamel M, et al. Early postnatal development of rat brain: in vivo diffusion tensor imaging. J Neurosci Res. 2008 5 15;86(7):1520–8. [PubMed: 18189320]
62. Kumar R, Nguyen HD, Macey PM, Woo MA, Harper RM. Regional Brain Axial and Radial Diffusivity Changes During Development. J Neurosci Res. 2012 2;90(2):346–55. [PubMed: 21938736]
63. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Front Hum Neurosci. 2014 8 19;8:584. [PubMed: 25191243]
64. Ruotsalainen I, Gorbach T, Perkola J, Renvall V, Syväoja HJ, Tammelin TH, et al. Physical activity, aerobic fitness, and brain white matter: Their role for executive functions in adolescence. Dev Cogn Neurosci. 2020 4 1;42:100765. [PubMed: 32072938]
65. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011 2 15;108(7):3017–22. [PubMed: 21282661]
66. Etnier JL, Wideman L, Labban JD, Piepmeier AT, Pendleton DM, Dvorak KK, et al. The Effects of Acute Exercise on Memory and Brain-Derived Neurotrophic Factor (BDNF). J Sport Exerc Psychol. 2016 8;38(4):331–40. [PubMed: 27385735]
67. Moon HY, Becke A, Berron D, Becker B, Sah N, Benoni G, et al. Running-induced systemic Cathepsin B secretion is associated with memory function. Cell Metab. 2016 8 9;24(2):332–40. [PubMed: 27345423]
68. Park H-S, Park S-S, Kim C-J, Shin M-S, Kim T-W. Exercise Alleviates Cognitive Functions by Enhancing Hippocampal Insulin Signaling and Neuroplasticity in High-Fat Diet-Induced Obesity. Nutrients. 2019 7;11(7):1603.
69. Jeong J-H, Koo J-H, Cho J-Y, Kang E-B. Neuroprotective effect of treadmill exercise against blunted brain insulin signaling, NADPH oxidase, and Tau hyperphosphorylation in rats fed a high-fat diet. Brain Res Bull. 2018;142:374–83. [PubMed: 30081082]
70. Sauder KA, Hockett CW, Ringham BM, Glueck DH, Dabelea D. Research: Epidemiology Fetal overnutrition and offspring insulin resistance and β-cell function: the Exploring Perinatal Outcomes among Children (EPOCH) study. Diabet Med J Br Diabet Assoc. 2017 10;34(10):1392–9.
71. Cockcroft EJ, Williams CA, Tomlinson OW, Vlachopoulos D, Jackman SR, Armstrong N, et al. High intensity interval exercise is an effective alternative to moderate intensity exercise for improving glucose tolerance and insulin sensitivity in adolescent boys. J Sci Med Sport. 2015 11;18(6):720–4. [PubMed: 25459232]
72. Jelleyman C, Edwardson CL, Henson J, Gray LJ, Rowlands AV, Khunti K, et al. Associations of Physical Activity Intensities with Markers of Insulin Sensitivity. Med Sci Sports Exerc. 2017 12;49(12):2451–8. [PubMed: 28723844]
73. Rynders CA, Weltman JY, Jiang B, Breton M, Patrie J, Barrett EJ, et al. Effects of exercise intensity on postprandial improvement in glucose disposal and insulin sensitivity in prediabetic adults. J Clin Endocrinol Metab. 2014 1;99(1):220–8. [PubMed: 24243632]
74. Belcher BR, Berrigan D, Dodd KW, Emken BA, Chou C-P, Spuijt-Metz D. Physical Activity in US Youth: Impact of Race/Ethnicity, Age, Gender, & Weight Status. Med Sci Sports Exerc. 2010 12;42(12):2211–21. [PubMed: 21084930]

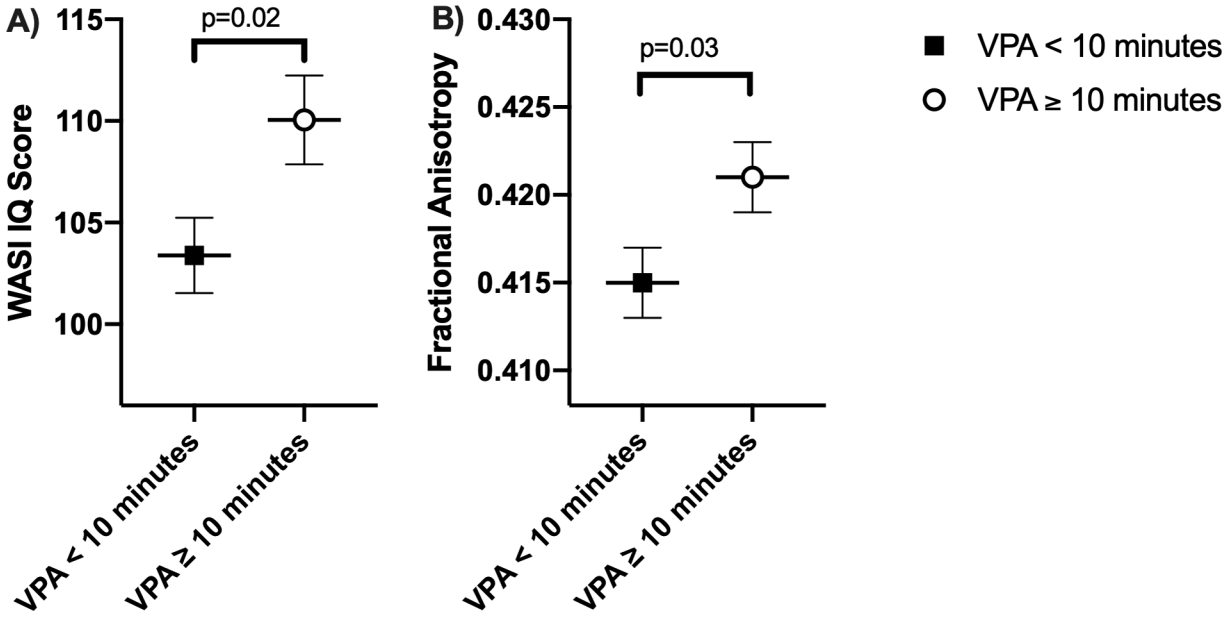

Figure 1.

Least Square mean IQ scores (Part A) and global FA (Part B) for children above and below median VPA

Abbreviations: IQ, intelligence quotient. FA, fractional anisotropy. VPA, vigorous physical activity. Least square means adjusted for child age, sex, BMI z-score, family income, maternal education and maternal pre-pregnancy BMI. VPA < 10 minutes, N=47; VPA ≥ 10 minutes, N=53.

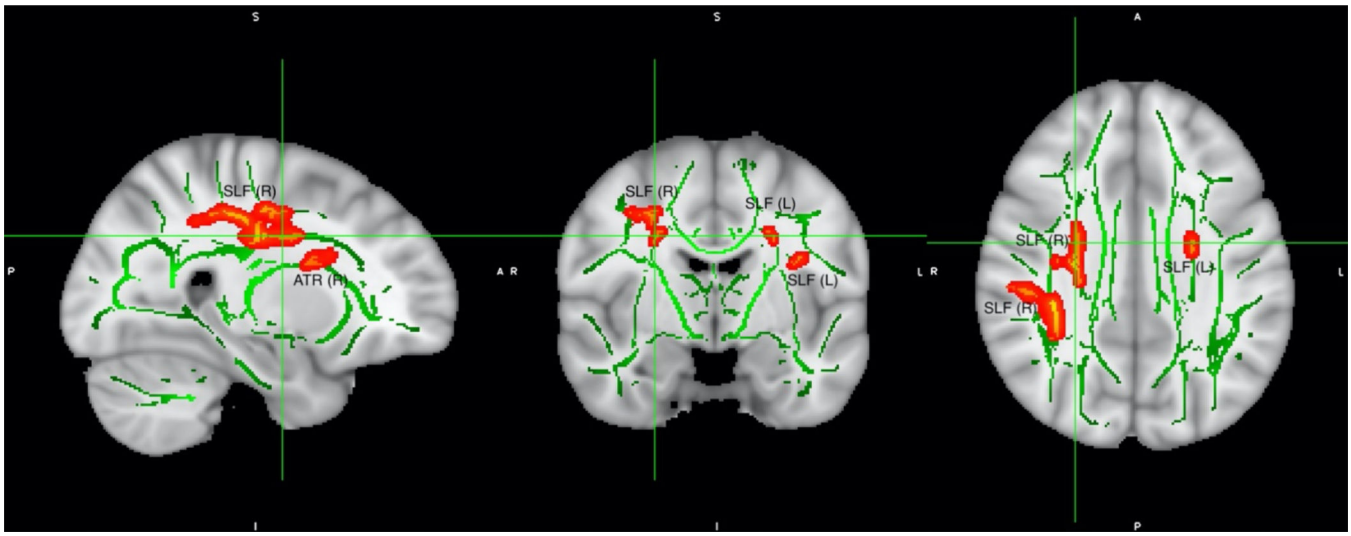

Figure 2.

TBSS results show clusters where FA was greater for children who engaged in above the median VPA compared to children below the median VPA

Sagittal, coronal and axial view of TBSS results. Regions in red/yellow show clusters where FA was greater in children who engaged in above the median VPA compared to below the median VPA, overlaid on a T1-weighted image with the mean FA skeleton (green). Results are adjusted for child age and sex and maternal pre-pregnancy BMI. Threshold set to $p<0.05$, family-wise error rate used to control for multiple comparisons. Abbreviations: TBSS, tract-based spatial statistics; FA, fractional anisotropy; VPA, vigorous physical activity.

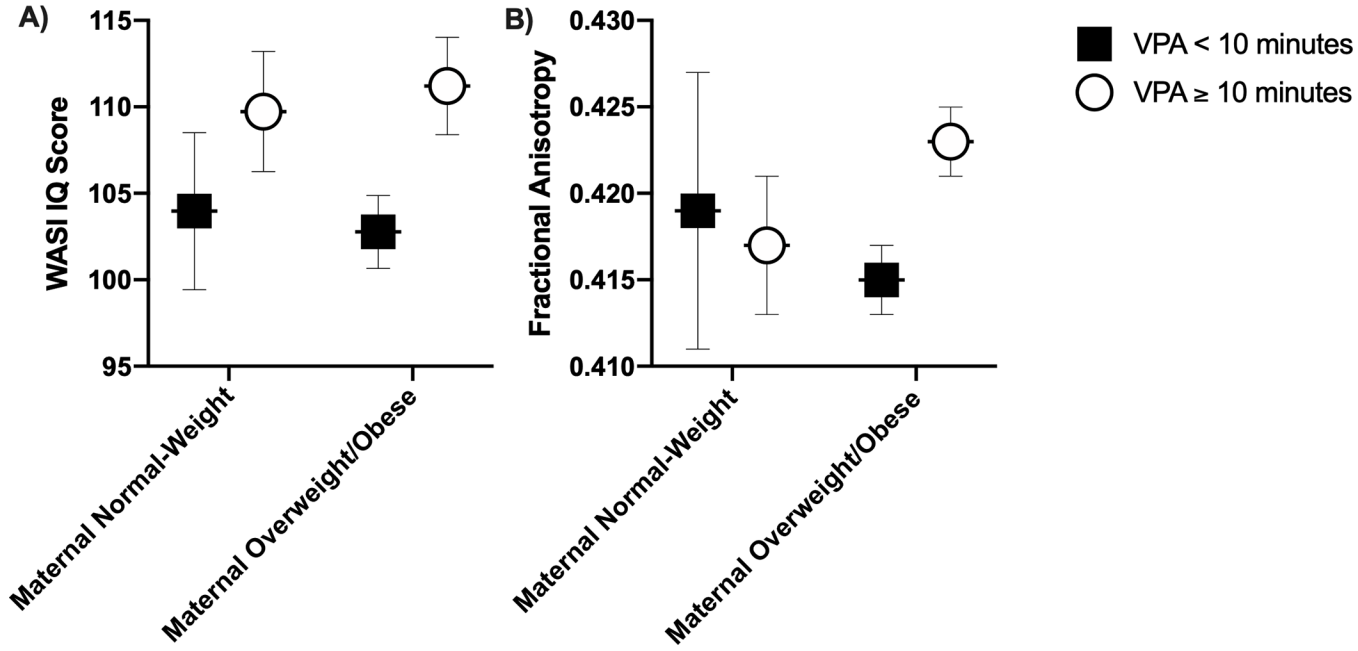

Figure 3.

Interaction between maternal pre-pregnancy weight status and VPA levels on child IQ score (Part A) and global FA (Part B)

Maternal normal-weight with VPA < 10 minutes (N=9), Maternal Overweight/Obese with VPA < 10 minutes (N=38); Maternal normal-weight with VPA ≥ 10 minutes (N=15), Maternal Overweight/Obese with VPA ≥ 10 minutes (N=38). Abbreviations: IQ, intelligence quotient. FA, fractional anisotropy. VPA, vigorous physical activity. Least square means adjusted for child age, sex, BMI z-score, family income, and maternal education.

Table 1.

Participant and Mother's Characteristics (N=100)

Variable	N (%) or Mean (SD)	Range
Age (years)	8.51 (1.00)	7.33 to 11.34
Sex	Girls: 59 (59%)	
	Boys: 41 (41%)	
Tanner Stage	Stage 1: 91 (91%)	
	Stage 2: 6 (6%)	
	Stage 3: 3 (3%)	
BMI z-score	0.75 (1.09)	−1.78 to 2.64
Child BMI Percentile Category	Healthy-weight: 60 (60%)	
	Overweight: 16 (16%)	
	Obese: 24 (24%)	
Median Time in LPA (min/day)	60 minutes	0 to 160
Median Time in MVPA (min/day)	100 minutes	0 to 430
Median Time in VPA (min/day)	10 minutes	0 to 270
WASI IQ Scores	108.80 (13.74)	76 to 150
Maternal Pre-pregnancy BMI (kg/m^2)	30.08 (7.11)	18.97 to 50.38
Maternal Pre-pregnancy Category	Normal-weight: 24 (24%)	
	Overweight: 35 (35%)	
	Obese: 41 (41%)	
Maternal Education at Birth	<=High school: 21 (21%)	
	Some college: 32 (32%)	
	College and post: 47 (47%)	
Family Income at Birth	0<=income <30 000: 15 (15%)	
	30 000<=income <50 000: 30 (30%)	
	50 000<=income <70 000: 30 (30%)	
	70 000<=income <90 000: 14 (14%)	
	90 000>=income: 11 (11%)	

Abbreviations: Age, child age. Time in MVPA, time in moderate-to-vigorous physical activity. Time in LPA, time in light physical activity. Time in VPA, time in vigorous physical activity. IQ, intelligence quotient.

Table 2.

Relationship between Maternal Pre-Pregnancy BMI or Physical Activity with Child IQ and Global FA (N=100)

Predictor Variables	Outcome Variables	Beta (95% CI)	p-value	Covariates
Maternal pre-pregnancy BMI	IQ Score	−0.31 (−0.67, 0.06)	0.10	Unadjusted
	Global FA	−0.00005 (−0.0004, 0.0003)	0.92	
	IQ Score	−0.24 (−0.63, −0.14)	0.22	age, sex, SES
	Global FA	−0.00005 (−0.0004, 0.0003)	0.81	
	IQ Score	−0.38 (−0.79, 0.03)	0.07	age, sex, SES, BMI z-score
	Global FA	−0.00005 (−0.0004, 0.0003)	0.80	
Time in LPA (min/day)	IQ Score	0.11 (−0.89, 1.12)	0.82	Unadjusted
	Global FA	−0.0006 (−0.0016, 0.0004)	0.24	
	IQ Score	−0.03 (−1.04, 0.98)	0.96	age, sex, SES
	Global FA	−0.0004 (−0.0004, 0.0006)	0.48	
	IQ Score	−0.08 (−1.09, 0.92)	0.87	age, sex, SES, BMI z-score, pre-pregnancy BMI
	Global FA	−0.0004 (−0.0014, 0.0006)	0.47	
Time in MVPA (min/day)	IQ Score	2.67 (−0.98, 6.24)	0.16	Unadjusted
	Global FA	−0.001 (−0.005, 0.002)	0.42	
	IQ Score	3.75 (0.12, 7.38)	0.05	age, sex, SES
	Global FA	−0.001 (−0.005, 0.002)	0.51	
	IQ Score	3.90 (0.33, 7.48)	**0.04** *	age, sex, SES, BMI z-score, pre-pregnancy BMI
	Global FA	−0.001 (−0.005, 0.002)	0.50	
Time in VPA (min/day)	IQ Score	7.05 (2.49, 11.60)	**0.003** *	Unadjusted
	Global FA	0.0009 (0.0002, 0.0017)	**0.02** *	
	IQ Score	6.08 (1.31, 10.84)	**0.01** *	age, sex, SES
	Global FA	0.0011 (0.0004, 0.0018)	**0.005** *	
	IQ Score	5.03 (0.13, 9.94)	0.05	age, sex, SES, BMI z-score, pre-pregnancy BMI
	Global FA	0.0011 (0.0004, 0.0018)	**0.005** *	

* P-values <0.05

Abbreviations: Age, child age. SES, socioeconomic status at birth (family income and maternal education). Time in LPA, time in light physical activity. Time in MVPA, time in moderate to vigorous physical activity Time in VPA, time in vigorous physical activity. IQ, intelligence quotient. FA, fractional anisotropy.

Table 3.

Relationship between Maternal Pre-Pregnancy BMI Weight Status (Normal-Weight vs. Overweight/Obese) with Child IQ and Global FA stratified by VPA levels.

Outcome Variable	Maternal Weight-status	VPA Category	N	Beta (95% CI)	p-value
IQ score	Maternal Normal-weight	VPA Category < 10 minutes	9	**Reference**	
	Maternal Overweight/Obese		38	**Reference**	
	Maternal Normal-weight	VPA Category ≥ 10 minutes	15	5.76 (−4.52, 16.03)	0.29
	Maternal Overweight/Obese		38	8.44 (1.43, 15.46)	**0.02** *
Global FA	Maternal Normal-weight	VPA Category < 10 minutes	9	**Reference**	
	Maternal Overweight/Obese		38	**Reference**	
	Maternal Normal-weight	VPA Category ≥ 10 minutes	15	−0.002 (−0.017, 0.013)	0.79
	Maternal Overweight/Obese		38	0.008 (0.002, 0.014)	**0.007** *

* P-values <0.05

Models adjusted for child age, sex, SES and BMI z-score.

Abbreviations VPA, vigorous physical activity, SES, family income, and maternal education.