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Original article

Early life factors and white matter microstructure in children with overweight and obesity: The ActiveBrains project

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SUMMARY

Background & aims: Exposure to a suboptimal environment during the fetal and early infancy period's results in long-term consequences for brain morphology and function. We investigated the associations of early life factors such as anthropometric neonatal data (i.e., birth length, birth weight and birth head circumference) and breastfeeding practices (i.e., exclusive and any breastfeeding) with white matter (WM) microstructure, and ii) we tested whether WM tracts related to early life factors are associated with academic performance in children with overweight/obesity.

Methods: 96 overweight/obese children (10.03 ± 1.16 years; 38.7% girls) were included from the Active-Brains Project. WM microstructure indicators used were fractional anisotropy (FA) and mean diffusivity (MD), derived from Diffusion Tensor Imaging. Academic performance was evaluated with the Battery III Woodcock–Muñoz Tests of Achievement. Regression models were used to examine the associations of the early life factors with tract-specific FA and MD, as well as its association with academic performance.

Results: Head circumference at birth was positively associated with FA of the inferior fronto-occipital fasciculus tract (0.441; $p = 0.005$), as well as negatively associated with MD of the cingulate gyrus part of cingulum (−0.470; $p = 0.006$), corticospinal (−0.457; $p = 0.005$) and superior thalamic radiation tract (−0.476; $p = 0.001$). Association of birth weight, birth length and exclusive breastfeeding with WM microstructure did not remain significant after false discovery rate correction. None tract related to birth head circumference was associated with academic performance (all $p > 0.05$).

Conclusions: Our results highlighted the importance of the perinatal growth in WM microstructure later in life, although its possible academic implications remain inconclusive.

1. Introduction

The period between conception and 2 years of age has been recognized as a critical stage for later health [1] as well as for brain development [2,3]. Exposure to a suboptimal environment during the fetal and early infancy periods results in long-term consequences for brain morphology and function [2,4,5]. In this line, several markers of perinatal nutrition and growth such as anthropometric neonatal data (i.e. weigh, length and head circumference at birth) and infant feeding practices (i.e.,

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breastfeeding practices and formula feeding) have been associated with brain development during childhood [6–8], as well as with neurocognitive outcomes [9].

Diffusion tensor imaging (DTI) is a neuroimaging technique that allows characterizing water diffusion patterns for in-vivo investigation of brain white matter (WM) microstructure [7]. Fractional anisotropy (FA) and mean diffusivity (MD) are the two main indicators derived from DTI. While FA is related to myelination and fiber organization of WM tracts, representing WM maturation; MD is an indicator that represents the average of water diffusion in all directions, representing poor WM maturation [10,11]. In turn, WM microstructure has been related to executive function and academic abilities in different populations [8,12,13].

Small size for gestational age, preterm birth, and low length and head circumference at birth may be the result of intrauterine growth restriction, and have been related to obesity risk and poor WM maturation [3,14–16]. For instance, infants with low birth weight show lower values of FA and higher values of MD during the first day of life [17]. In addition, large size for gestational age at birth has been consistently related to higher values of FA and lower values of MD in several WM tracts (e.g., corticospinal, inferior fronto-occipital fasciculus, corona radiata) of infants across the wide spectrum of gestational age [3,14]. Of note, few studies have investigated the associations of neonatal anthropometric indices with long-lasting WM microstructure later in life [10,18–23], and most of them focused on birth weight. For example, children born with low birth weight had lower FA values in specific projection or association tracts (e.g., forceps minor and superior longitudinal fasciculus), but not in global FA [24]. Likewise, young adults born preterm with low birth weight had regional reduced FA and increased MD [21]. Further, there is a lack of studies investigating the specific association of birth length and birth head circumference with WM microstructure during childhood.

Breastfeeding provides important nutrients that are precursors of myelin and WM microstructure, and in turn, of cognitive development in the first stage of life [8,25]. The duration of breastfeeding has been associated with better regional, but no global WM maturation both in humans and non-human primates during childhood [26–28]. Despite this, only few studies have examined the long-lasting association of breastfeeding practices specifically on WM maturation, and robust conclusions have not been established so far.

Children with overweight/obesity showed reduced academic abilities, worse cardiorespiratory fitness (CRF) [29,30] and different patterns of WM maturation [31,32] compared to normal-weight children [28,33]. Interestingly, while there are previous studies showing the influence of CRF on WM maturation in normal weight and obese children [34,35], no studies have considered BMI or CRF when examining the influence of early life factors on WM maturation. Therefore, further studies investigating the association of early life factors, WM maturation and academic performance, including several confounder factors as BMI and CRF in children with overweight/obesity are needed.

The objectives were i) to investigate the associations of early life factors such as anthropometric neonatal data (i.e., birth length, birth weight and birth head circumference) and breastfeeding practices (i.e., exclusive and any breastfeeding) with WM microstructure, and ii) we test whether WM tract related to early life factors are associated with academic performance in children with overweight/obesity.

2. Method

2.1. Participants

We included 98 children with overweight/obesity (categorized based on the World Obesity Federation cut-off points) [36] aged 8–11 years from the ActiveBrains randomized clinical trial [37] (www.profith.ugr.es/activebrains). The present cross-sectional study was performed using baseline data prior to randomization. Measurements were carried out from November 2014 to February 2016. All included participants had valid data of early life factors, DTI metrics and academic performance variables (see Table 1 for n in each variable). Parents or legal guardians were informed of the purpose of the ActiveBrains study and parental written informed consents were obtained. The ActiveBrains project was registered in ClinicalTrials.gov (identifier: NCT02295072) and was approved by the Ethics Committee on Human Research of the University of Granada.

2.2. Early life factors

Height (kg), length (cm) and head circumference (cm) at birth were collected from health records (i.e., physical medical record that parents have with the offspring's perinatal information). The duration of both exclusive and any breastfeeding in months was reported by parents. Parents were asked the question: *for how long (months) did the child receive only breast milk (neither formula or other liquid or solid)?* This was considered as exclusive breastfeeding. Furthermore, they were also asked *for how long (months) did the child receive any breast milk (combined with other liquid, formula, or solid)?* This was considered as any breastfeeding. The responses were collected as continuous scale in months of breastfeeding.

2.3. Magnetic resonance imaging (MRI) procedure

2.3.1. Image acquisition

MRI data were acquired with a 3.0 T S Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany). The DTI sequence consisted of a 128 direction echo planar imaging (EPI) sequence using the following sequence parameters: TR = 3300 ms, TE = 90 ms, flip angle = 90, matrix = 128 × 128, FOV = 230 mm × 230 mm, slice thickness = 4 mm, number of slices = 25 and voxel resolution = 1.8 × 1.8 × 4 mm^3. 30 volumes with diffusion weighting (b = 1000 s/mm^2) were collected and one volume without diffusion weighting (b = 0 s/mm^2).

2.3.2. Image quality assurance

Raw image quality was checked with a visual inspection. The sum of squares error (SSE) maps from the tensor estimation was calculated and visually inspected for structured noise. Image quality was rated using a 4-point scale, with 1 = “excellent”, 2 = “minor”, 3 = “moderate”, and 4 = “severe”. Two subjects were manually excluded to be of insufficient quality (i.e., moderate and severe) due to poor image quality. Finally, probabilistic tractography data were visually inspected. First, the native space FA map registration was inspected to ensure images were all properly aligned to the template (masks were properly mapped to native space). Second, all tracts were visualized to ensure accurate path reconstruction.

Table 1
Characteristics of the study sample.

	All		*Boys*		*Girls*	
N	*n*		*n*		*n*	
Physical characteristics	98		60		38	
Age (yr)		10.03 ± 1.16		10.15 ± 1.18		9.81 ± 1.10
Weight (kg) [29.9–78.8]		55.52 ± 11.22		56.55 ± 10.99		53.87 ± 11.53
Height (cm) [8–11.99]		143.9 ± 8.56		144.78 ± 7.92		142.59 ± 9.44
PHV (yr) [-4.18 − 0.3]		−2.30 ± 0.98		−2.64 ± 0.82		−1.76 ± 0.99
CRF (mL/kg/min)[a] [34.8–48.5]		40.86 ± 2.72		40.85 ± 2.67		40.88 ± 2.73
BMI (kg/m^2) [19.7–36.5]		26.58 ± 3.64		26.79 ± 3.76		26.24 ± 3.47
Body mass index category (%)	98		60		38	
Overweight		27.6		26.7		28.9
Obesity type I		42.9		46.7		36.8
Obesity type II		29.6		26.7		34.2
Parental education university level (%)	98		60		38	
None of the parents		65.3		70.0		57.9
One of the two parents		18.4		16.7		21.1
Both parents		16.3		13.3		21.1
Neonatal characteristics						
Birth weight (g) [1370–4600]	96	3325.31 ± 549.13	59	3337.11 ± 597.30	37	3306.48 ± 469.41
Birth length (cm) [40–57]	87	50.68 ± 2.67	57	50.60 ± 3.06	30	50.86 ± 1.77
Gestational age (week) [26–43]	98	38.58 ± 2.63	60	38.50 ± 2.69	38	38.69 ± 2.56
Birth head circumference [25–38]	51	34.51 ± 2.01	32	34.57 ± 2.35	19	34.38 ± 1.31
Exclusive breastfeeding[b](%)	94		59		35	
Never		31.9		28.8		37.1
< 3 months		16.0		18.6		11.4
3–5 months		25.5		20.3		34.3
≥ 6 months		26.6		32.2		17.1
Any breastfeeding[c] (%)	95		59		36	
Never		21.1		20.3		22.2
< 3 months		12.6		11.9		13.9
3–5 months		26.3		23.7		30.6
≥ 6 months		40.0		44.1		33.3
Academic performance (standard score)[d]	98		60		38	
Mathematics		102.49 ± 10.64		103.0 ± 11.1		10.00 ± 9.97
Reading		108.90 ± 12.89		109.0 ± 11.2		109.00 ± 15.3
Writing		114.70 ± 12.12		113.0 ± 11.8		117.0 0 ± 12.3
Total Achievement		110.10 ± 11.65		110.0 ± 10.7		111.00 ± 13.1

Values are mean ± SD or percentage.
[a] Measured with the 20-m shuttle run test.
[b] Months the child received only breast milk.
[c] Months the child received breast milk combined with other liquids, or solids.
[d] Measured by the Battery III Woodcock-Muñoz Tests of Achievement. PHV: Peak height velocity offset; CRF: Cardiorespiratory fitness; BMI: Body mass index.

2.3.3. Image preprocessing

Functional MRI of the Brain's Software Library (FSL) (https://fsl.fmrib.ox.ac.uk) was used for image preprocessing [38,39]. First, image was adjusted for minor head motion and eddy-current induced artifacts [40,41]. In order to account for rotations applied to the image data [42,43], the resulting transformation matrices were used to rotate the diffusion gradient. Non-brain tissue was removed using the FSL Brain Extraction Tool [44]. Then, the diffusion tensor was fit, and common scalar maps (e.g., FA and MD) were subsequently computed. Detailed information about preprocessing steps is described elsewhere [45].

2.3.4. Probabilistic fiber tractography

Diffusion tensor data were first processed using the Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTx), accounting for two fiber orientations at each voxel [46,47]. Next, for each subject, the FA map was aligned to the FMRIB-58 FA template image with the FSL nonlinear registration tool (FNIRT). The inverse of this nonlinear warp field was computed and applied to a series of predefined seed, target, exclusion, and termination masks provided by the AutoPtx plugin. Probabilistic fiber tracking was then performed with the FSL Probtrackx module using these supplied tract-specific masks (i.e., seed, target, etc.) that were warped to the native diffusion image space of each subject [46]. The resulting path distributions were normalized to a scale from 0 to 1 using the total number of successful seed-to-target attempts and were subsequently thresholded, based on previous studies, to remove low-probability voxels likely related to noise. FA and MD values for these tracts were estimated for 15 large fiber bundles separately for left and right hemispheres (see Table 2) [48].

2.4. Academic performance

The Battery III Woodcock–Muñoz Tests of Achievement was used to assess academic performance (i.e., Spanish version of the Woodcock-Johnson III) [49]. A trained evaluator individually administered the tests to each child. The full administration time was between 100 and 120 min. In this study, we included standard score indicators of reading, writing mathematics and total achievement.

2.5. Covariates

Gestational age (weeks) was collected from birth records; pubertal maturity status was determined by peak height velocity (PHV) and was obtained through the Moore et al. equation for boys and girls [50]; PHV offset was calculated by the difference

Table 2
Association of birth length, birth weight and birth head circumference with fractional anisotropy (FA) and mean diffusivity (MD) of the white matter microstructure.

	Birth length				Birth weight				Birth head circumference			
	FA		MD		FA		MD		FA		MD	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Acoustic Radiation	0.234	0.052	−0.191	0.112	0.064	0.591	−0.08	0.498	**0.38**	**0.029**	−0.134	0.446
Anterior thalamic radiation	0.196	0.09	−0.204	0.08	0.081	0.484	0.004	0.971	**0.445**	**0.011**	−0.151	0.361
Cingulate gyrus part of cingulum	**0.276**	**0.030**	−0.199	0.115	**0.28**	**0.022**	−0.086	0.483	0.170	0.412	**−0.470**	**0.006***
Hippocampal part of the cingulum	0.046	0.711	−0.012	0.918	0.046	0.704	−0.006	0.96	−0.063	0.721	0.316	0.061
Corticospinal tract	0.134	0.255	−0.171	0.141	−0.045	0.695	−0.092	0.421	0.308	0.068	**−0.457**	**0.005***
Inferior fronto-occipital fasciculus	**0.320**	**0.006**	−0.166	0.149	0.156	0.177	0.025	0.823	**0.441**	**0.005***	−0.136	0.397
Inferior longitudinal fasciculus	**0.263**	**0.023**	−0.094	0.407	0.109	0.342	0.103	0.352	**0.409**	**0.011**	−0.033	0.838
Medial lemniscus	0.142	0.241	−0.16	0.192	0.149	0.202	−0.209	0.08	0.256	0.158	−0.286	0.112
Posterior thalamic radiation	0.157	0.175	−0.193	0.092	−0.074	0.518	−0.075	0.502	0.223	0.191	−0.170	0.275
Superior longitudinal fasciculus	0.121	0.305	−0.224	0.055	−0.046	0.689	−0.087	0.45	0.275	0.082	**−0.310**	**0.036**
Superior thalamic radiation	0.153	0.188	−0.205	0.070	−0.050	0.666	−0.068	0.55	0.246	0.157	**−0.476**	**0.001***
Uncinate fasciculus	0.166	0.169	**−0.255**	**0.032**	0.162	0.173	−0.087	0.461	0.227	0.190	−0.151	0.392
Forceps major	−0.048	0.692	−0.036	0.762	−0.091	0.443	0.042	0.718	0.031	0.864	0.139	0.402
Forceps minor	0.044	0.712	0.014	0.907	0.022	0.848	−0.03	0.797	−0.026	0.884	−0.283	0.097
Middle cerebellar peduncle	−0.053	0.654	−0.058	0.623	0.014	0.905	−0.123	0.282	**0.400**	**0.022**	−0.132	0.453

Lineal regression models were adjusted for sex, peak height velocity, gestational age, parental education level, body mass index and cardiorespiratory fitness. FA= Fractional anisotropy (high FA corresponds to preferential diffusion along one direction indicating a high level of tissue organization), MD = mean diffusivity (high MD corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization). Values of $p < 0.05$ are in bold. *Indicated that p value survived the FDR correction for multiple testing. β = Standardized values.

between PHV and chronological age. Parents were asked to report their maximum completed level of education and answers were categorized as: none of the parents had university degree, one of the parents had a university degree or both parents had a university degree. BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2). CRF was assessed through the 20-m shuttle-run test and maximal oxygen consumption (VO_2max, mL/kg/min) was calculated using the Lèger equation [51].

2.6. Statistical analysis

Participant's characteristics are shown as mean and standard deviation (SD) for continuous variables, and n and percentages for categorical variables. Multiple linear regressions were performed to test the associations between each early life factor such as anthropometric neonatal data (i.e., birth weight, birth length and birth head circumference), and feeding practices (i.e., exclusive and any breastfeeding) with FA and MD values of each WM tract, adjusted for sex, gestational age, PHV, parental education level, BMI (as raw data and z-score) and CRF. Since there were significant and robust correlations between hemispheres for most of the tracts (see correlation matrix in Supplementary Figs. 1 and 2), we averaged FA and MD values across left and right hemispheres. Because of the number of comparisons (15 per DTI metric), a false discovery rate (FDR) [52] correction was applied to the results of each early life factors across both FA and MD simultaneously (30 comparisons for each early life factor), using the "p.adjust" function in R. Then, multiple linear regressions were performed for those tracts associated with early life factors after FDR correction ($p < 0.05$) and academic performance (and executive function) adjusting for sex, PHV, parental education level, BMI and CRF. Finally, mutual adjustment between the significant anthropometric neonatal data (after FDR correction) and feeding practice (including covariates mentioned above) were performed. Sensitivity analyses were carried out excluding children born preterm (gestational age <37 weeks) and including total brain volume as covariate in the birth head circumference models.

All statistical analyses were performed using R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $p < 0.05$.

3. Results

Table 1 presents participant characteristics. Table 2 presents the associations of anthropometric neonatal data with tract-specific FA and MD. Birth length was positively associated with FA in the cingulate gyrus part of cingulum, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus tract (β ranging from 0.263 to 0.320 and $p \leq 0.030$), and negatively with MD in uncinate fasciculus tracts ($p < 0.05$). Birth weight was positively associated with FA in the cingulate gyrus part of cingulum tract ($\beta = 0.280$ and $p \leq 0.022$). Finally, birth head circumference was positively associated with FA in several tracts: acoustic radiation, anterior thalamic radiation, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and middle cerebellar peduncle (β ranging from 0.380 to 0.445 and $p \leq 0.029$), and it was negatively associated with MD in the cingulate gyrus part of cingulum, corticospinal tract, superior longitudinal fasciculus and superior thalamic radiation tracts (β ranging from −0.310 to 0.476 and $p \leq 0.036$). When we included total brain volume as covariate into the models with head circumference as main exposure (given its significant association with birth head circumference, $r = 0.44$, $p < 0.01$), results were virtually the same. However, after FDR correction, solely the associations of birth head circumference with FA in the inferior frontal-occipital fasciculus ($\beta = 0.441$; $p = 0.005$) and with MD in the cingulate gyrus part of cingulum, corticospinal tract and superior thalamic radiation tract remained significant (β ranging from −0.476 to −0.457 and $p \leq 0.006$).

Table 3 presents the associations of exclusive and any breastfeeding with tract-specific FA and MD, adjusted for CRF and BMI. Significant associations between exclusive breastfeeding and FA in the inferior longitudinal tract and parahippocampal part of cingulum fasciculus (β ranging from 0.221 to 0.259 and $p \leq 0.041$) disappeared after FDR correction. The results were repeated excluding children born preterm from the analyses did not substantially change (data not shown).

Figure 1 shows the associations between head circumference with WM after FDR correction. It was observed that head circumference was associated with FA in the inferior frontal-occipital fasciculus ($\beta = 0.43$ and $p = 0.009$), and with MD in the cingulate gyrus part of cingulum, corticospinal tract and superior thalamic radiation tract (β ranging from −0.52 to −0.50 and $p \leq 0.006$)

Table 3
Association of breastfeeding with fractional anisotropy (FA) and mean diffusivity (MD) of the white matter microstructure.

	Exclusive Breastfeeding				Any Breastfeeding			
	FA		MD		FA		MD	
	β	*p*	*β*	*p*	*β*	*p*	*B*	*p*
Acoustic Radiation	−0.047	0.678	0.097	0.379	0.086	0.42	0.042	0.687
Anterior thalamic radiation	0.005	0.964	0.023	0.832	0.046	0.666	0.079	0.447
Cingulate gyrus part of cingulum	0.055	0.633	0.084	0.459	0.134	0.226	0.098	0.366
Hippocampal part of the cingulum	0.009	0.939	0.017	0.879	0.123	0.258	−0.136	0.201
Corticospinal tract	0.133	0.219	−0.018	0.868	−0.009	0.93	0.114	0.262
Inferior fronto-occipital fasciculus	0.193	0.077	0.042	0.694	0.136	0.193	0.100	0.327
Inferior longitudinal fasciculus	**0.221**	**0.041**	0.080	0.443	0.187	0.071	0.139	0.162
Medial lemniscus	0.021	0.852	−0.037	0.744	−0.091	0.39	−0.014	0.895
Posterior thalamic radiation	**0.259**	**0.015**	0.042	0.689	0.135	0.191	0.128	0.196
Superior longitudinal fasciculus	0.206	0.058	0.002	0.986	0.142	0.174	0.043	0.674
Superior thalamic radiation	0.13	0.236	0.017	0.878	0.078	0.458	0.147	0.147
Uncinate fasciculus	0.029	0.797	−0.034	0.759	0.048	0.654	−0.045	0.672
Forceps major	0.206	0.065	−0.042	0.702	0.006	0.955	0.081	0.438
Forceps minor	−0.098	0.376	0.166	0.128	−0.121	0.252	0.143	0.171
Middle cerebellar peduncle	0.176	0.108	−0.025	0.819	0.107	0.308	−0.023	0.828

The lineal regression model was adjusted for sex, peak height velocity, gestational age, parental education level, body mass index and cardiorespiratory fitness. FA= Fractional anisotropy (high FA corresponds to preferential diffusion along one direction indicating a high level of tissue organization), MD = mean diffusivity (high MD corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization). Values of $p < 0.05$ are in bold. β = Standardized values. No p value survived the FDR correction.

regardless of sex, peak height velocity, gestational age, parental education level, BMI and CRF (model 1) exclusive breastfeeding duration (model 2).

Table 4 shows the association between tract previously related to birth head circumference (after FDR correction) and academic performance. No significant associations were found (all $p \geq 0.107$). Regarding cognitive measures (for more information about the tests see Mora-Gonzalez [53]), there were no significant associations between the tract previously related to birth head circumference and executive function indicators (all $p \geq 0.118$) (see Supplementary Table 2). Lastly, we repeated all the analyses included BMI z-score instead of raw BMI as covariate, and the results were not altered.

4. Discussion

The main findings of the present study indicate tract-specific associations between early life factors and WM maturation in children with overweight/obesity after adjusting for several covariates including BMI and CRF. Specifically, birth head circumference was positively associated with FA in the inferior fronto-occipital fasciculus, and negatively associated with MD in the cingulate gyrus part of cingulum, corticospinal and superior thalamic radiation. In addition, several WM tracts were modified as a function of birth weight and length as well as exclusive breastfeeding but did not remain after FDR correction. Lastly, WM tracts related to birth head circumference were not associated with academic performance. These results suggest that WM maturation during childhood could be partially influenced by the fetal environment in children with overweight/obesity, but the implicated behavioral consequences remain inconclusive.

Several mechanisms might be speculated to explain the present results. During the gestation period, several key processes help to develop WM microstructure, such as the growth and wiring of axonal fibers; indeed, a non-optimal pregnant environment might cause negative consequences for WM development. For example, oligodendrocytes sensitive to hypoxia, that are abundant after term and are precursors of myelin in axonal fibers, mostly occur during the second period of gestation. On the other hand, the pruning of useless connections rather starts during the first post-natal weeks along with external stimulations related to acute changes in myelination during the first post-natal months [54,55]. Of note, FA increases up to 44% during the first year, while the second year increases up to 9% over levels at age 1 year [2]. Although it is well established that WM is developed during prenatal period, certain regions continue their development through childhood and adolescence [56]. Lastly, a recent work suggests that exposure to perinatal risk factors is mainly related to reductions in cross-section of WM fiber more than to alterations in fiber density [57].

Regarding specific tract associations, head circumference at birth was positively associated with FA in the inferior fronto-occipital fasciculus. Although there is a lack of studies showing this association with birth head circumference in term-born children, similar differences have been found in neonates with different body size at birth [14,15,58]. For instance, head circumference was associated with WM maturation in the inferior fronto-occipital fasciculus in preterm children at term-equivalent age [58]. Also, those born preterm show lower FA in this tract in comparison with term-born children at school age [23] as well as in adolescence [22]. This suggests that the inferior fronto-occipital fasciculus is especially sensitive to insults of the gestational environment, and this is detectable even several years later. Previous studies suggest the possible implications of the inferior fronto-occipital fasciculus in several cognitive indicators. For instance, lower FA in the inferior fronto-occipital fasciculus has been related to poorer cognition [59], since it connects multiple regions involved in critical cognitive functions (i.e., language and reading development) [19], such as occipital to the temporal and frontal lobe [60]. Further, recent findings also suggest that the inferior fronto-occipital fasciculus plays a crucial role in both verbal and non-verbal semantic cognition [61] as well as face processing [60] or goal-oriented behavior [62].

Conversely, birth head circumference was negatively associated with MD of the cingulate gyrus part of cingulum, corticospinal tract and superior thalamic radiation. We did not find studies reporting this specific association in term-born children. Instead, these tracts have been associated with other anthropometric birth indicators both in the newborn, as well as during childhood and adulthood. For instance, prematurity and low birth weight have been associated with reduced WM integrity in the corticospinal tract and superior thalamic radiation in the newborn [14,63]. On the other hand, there was a long-lasting relation between preterm and WM integrity in the corticospinal tract in childhood [20,23]. In addition,

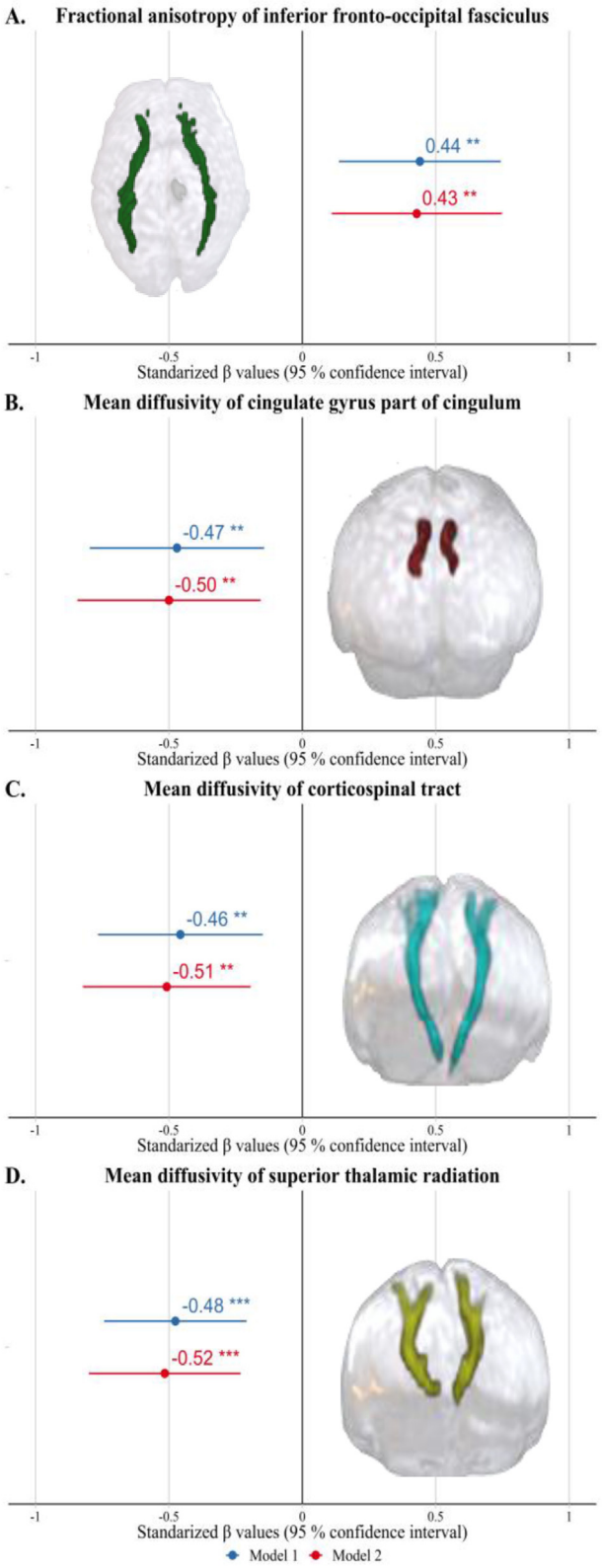

Fig. 1. The associations between birth head circumference with white matter tracts after FDR correction with additional adjustment for feeding practices. Model 1: adjusted for sex, peak height velocity, gestational age, parental education level, body mass index and cardiorespiratory fitness. Model 2: Model 1 plus exclusive breastfeeding. Tract images are representative of one random subject of our sample.

very low birth weight infants showed poorer WM organization (increased MD) in the cingulate gyrus part of cingulum [64] and the corticospinal tract even in adulthood [65]. Our findings suggest that the association of head circumference with WM microstructure in central brain regions such as the corticospinal tract and the superior thalamic radiation persists until childhood. Similarly, Eikenes et al. demonstrate the effect of poor anthropometric neonatal data on WM integrity persists beyond childhood to adulthood, even affecting other peripheral tracts [21].

Importantly, associated tracts may have different behavioral implications during childhood. The cingulate gyrus part of cingulum is a major limbic WM pathway linking cortical regions and amygdala, and it is involved in cognitive control, affect and emotion regulation, and face processing [66,67]. It is well recognized that the corticospinal tract is a principal motor pathway for voluntary movements, and that it is involved in fine movements of the distal extremities [68–70], as well as the implication of the superior thalamic radiation tract in the relationship of sensory-motor cortex [70,71]. Of note, it has been reported that the corticospinal tract is one of the most mature WM tracts during the first months after birth, since projection fibers start to develop in the first trimester of pregnancy [54,68,72]. Lastly, the motor cortex is one of the specific region influenced by the perinatal period, being a common site of brain damage to occur [70].

Interestingly, previous studies reported that the development of WM starts from the center to the periphery of the brain and from the occipital lobe towards the frontal lobe, with a posterior to anterior development [68,73]. Indeed, this WM microstructural changes might be responsible for neurodevelopmental deficits in cognitive and motor functions [63]. Here, we tested the association of changes of WM maturation due to suboptimal early life factors on academic performance, according to previous studies that suggested its implication in executive function and academic abilities [8,12,13]. Conversely, we did not find tracts (previously associated with birth head circumference) associated with academic performance as well as executive function in children with overweight/obesity children; future studies in larger samples should examine other possible implications in sensory-motor function, emotion regulation or face recognition.

Although it is well established that breastfeeding is an important precursor of key nutrients associated with WM development, we did not find any association of breastfeeding practices and WM maturation in children with overweight/obesity. Likewise, a previous work in a similar age range found that breastfeeding duration was not associated with WM volumes [74], and another work found a significant association between exclusive breastfeeding duration and WM microstructure in boys, but not in girls [75]. Thus, it is possible that obesity is masking the effect of breastfeeding on WM and that the plausible effects of breastfeeding practices are not detectable in childhood. However, further studies including both normal-weight and children with overweight/obesity are needed to confirm or refute this hypothesis.

4.1. Limitations

The current study has some limitations that must be mentioned. The use of a retrospective cross-sectional design prevents us from inferring causal relationships. In addition, our analyses need replication in larger samples to elucidate the associations between the different early life factors and WM maturation in both children with overweight/obesity. In this line, the extent to which the findings from our study conducted in

Table 4
Associations of white matter tract related to birth head circumference with academic performance.

	Mathematics		Reading		Writing		Total achievement	
	B	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Fractional Anisotropy								
IFOF	−0.227	0.107	0.021	0.881	−0.146	0.334	−0.125	0.374
Mean Diffusivity								
CGC	0.258	0.114	0.200	0.245	0.115	0.516	0.242	0.141
CST	−0.112	0.400	0.010	0.941	0.021	0.881	−0.022	0.867
STR	−0.114	0.444	−0.202	0.166	0.089	0.573	−0.123	0.401

Lineal regression models were adjusted for sex, peak height velocity, parental education level, body mass index and cardiorespiratory fitness. Fractional anisotropy corresponds to preferential diffusion along one direction indicating a high level of tissue organization, and mean diffusivity corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization). Academic performance was measured with the Battery III Woodcock-Muñoz Tests of Achievement. β = Standardized values. IFOF: Inferior fronto-occipital fasciculus, CGC: Cingulate gyrus part of cingulum, CST: Corticospinal tract, STR: Superior thalamic radiation.

children with overweight/obesity applies to other populations of different characteristics such as children with normal body weight status is matter of future investigations. On the other hand, we did not collect information about important confounding factors during the pregnant environment as well as the type of complementary feeding or feeding following the breast- or formula-feeding period, and null results about breastfeeding might be explained by the differences in these dietary patterns and other lifestyle indicators not controlled during the first years of life. Further, although DTI-derived measurements provide valuable information about WM microstructure, caution needs to be taken when interpreting the results. It is well known that interpretation of FA is complex and diffusivity measurements are at most indirect indicators of myelination, axon packing, membrane permeability or axon density [76,77], and diffusion can be influenced by numerous factors [78,79] that FA cannot differentiate. In this line, our resolution was 4 mm^3 and has been documented that in an isotropic resolution ≥2 mm, FA can be affected by crossing fibers [76]. Additionally, our tract-specific approach did not have tract-specific masks for all brain regions. For instance, we did not encompass the corpus callosum outsize of the forceps major and forceps minor fiber bundles. Despite the noted limitations, this study has several strengths such as the inclusion of BMI, CRF, socioeconomic status and pubertal maturity status as covariates, the use of a reliable measurement of academic performance, the relatively large sample of children with overweight/obesity with DTI measurements and its bounded range of age.

4.2. Conclusion

Our findings suggest that out of the different perinatal factors studied, only birth head circumference was associated with selected WM tracts Specifically, birth head circumference was associated with inferior fronto-occipital fasciculus, cingulate gyrus part of cingulum, corticospinal and superior thalamic radiation tracts. Lastly, WM tracts related to birth head circumference were not associated with academic performance, other behavioral implications remain a matter of speculation. These results highlight the importance of the perinatal growth in WM microstructure later in life and leave inconclusive its possible functional implications.

Conflict of Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.10.022.

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