Archival Report

Biological Psychiatry: CNNI

# Intrauterine Exposure to Antidepressants or Maternal Depressive Symptoms and Offspring Brain White Matter Trajectories From Late Childhood to Adolescence

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## ABSTRACT

**BACKGROUND:** During pregnancy, both selective serotonin reuptake inhibitor (SSRI) exposure and maternal depression have been associated with poor offspring neurodevelopmental outcomes. In a population-based cohort, we investigated the association between intrauterine exposure to SSRIs and depressive symptoms and offspring white matter development from childhood to adolescence.

**METHODS:** Self-reported SSRI use was verified by pharmacy records. In midpregnancy, women reported on depressive symptoms using the Brief Symptom Inventory. Using diffusion tensor imaging, offspring white matter microstructure, including whole-brain and tract-specific fractional anisotropy (FA) and mean diffusivity, was measured at 3 assessments between ages 7 to 15 years. The participants were divided into 4 groups: prenatal SSRI exposure ($n$ = 37 with 60 scans), prenatal depression exposure ($n$ = 229 with 367 scans), SSRI use before pregnancy ($n$ = 72 with 95 scans), and reference ($n$ = 2640 with 4030 scans).

**RESULTS:** Intrauterine exposure to SSRIs and depressive symptoms were associated with lower FA in the whole-brain and the forceps minor at 7 years. Exposure to higher prenatal depressive symptom scores was associated with lower FA in the uncinate fasciculus, cingulum bundle, superior and inferior longitudinal fasciculi, and corticospinal tracts. From ages 7 to 15 years, children exposed to prenatal depressive symptoms showed a faster increase in FA in these white matter tracts. Prenatal SSRI exposure was not related to white matter microstructure growth over and above exposure to depressive symptoms.

**CONCLUSIONS:** These results suggest that prenatal exposure to maternal depressive symptoms was negatively associated with white matter microstructure in childhood, but these differences attenuated during development, suggesting catch-up growth.

https://doi.org/10.1016/j.bpsc.2023.10.009

Approximately 7% to 20% of women experience depressive symptoms during pregnancy (1–4). Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacological treatment for depression. About 6% to 8% of pregnant women in the United States receive antidepressant therapy, primarily with SSRIs (1,5,6). The prevalence of prenatal SSRI use is lower in Northern Europe, approximately 1% to 2% (7). Pregnant women with depressive symptoms often take SSRIs during pregnancy to avoid relapse (i.e., maintenance treatment). However, concerns about the potential adverse effects on child development have arisen (8). Consistent with this, in one study, about 50% of pregnant women who were prescribed SSRIs preconceptionally discontinued use during pregnancy, potentially putting them at an increased risk of psychiatric problems (9). Depression during pregnancy poses significant risks to mothers and their offspring. Therefore, decision making about antidepressant use during pregnancy is challenging because both prenatal SSRI exposure and maternal depressive symptoms may have a negative impact on offspring development (8,10). Prenatal exposure to SSRIs and maternal depression have been associated with poor neurodevelopmental outcomes in children, including emotional and behavioral difficulties (11,12), lower IQ (13,14), and problems with motor development (15,16) and speech/language and school achievements (17–19). However, the underlying pathways are not yet fully understood (20,21).

White matter maturation is prolonged, dynamic, and vulnerable to early-life exposures, potentially impacting offspring functioning via this pathway (22). Neuroimaging can be used to study white matter development to better understand the neurobiology that underlies these associations. To date, most neuroimaging studies of prenatal exposure to SSRIs and depressive symptoms in offspring have been cross-sectional studies with small samples ($n$ = 14 to 27 infants), and the results have been inconsistent (20,21). Diffusion tensor imaging (DTI) studies in neonates that have investigated the





ISSN: 2451-9022

association between prenatal SSRI use and white matter microstructure are sparse. Intrauterine SSRI exposure has been related to lower fractional anisotropy (FA) compared with matched control participants across multiple fiber bundles (e.g., the corticofugal and corticothalamic projection tracts) (23). Lugo-Candelas *et al.* (24) reported higher FA within the amygdala-insula circuitry in SSRI-exposed newborns than in nonexposed control participants. Furthermore, DTI studies in neonates and young children suggested that prenatal depressive symptoms are associated with lower connectivity of white matter microstructures in the amygdala, prefrontal cortex, and corpus callosum (25–30). Previous work in our research group showed that prenatal maternal depressive symptoms were associated with higher mean diffusivity (MD) in the uncinate fasciculus as well as lower FA and higher MD in the cingulum bundle in offspring ages 6 to 9 years (31) and with lower FA in the forceps minor at age 10 years (32). To better comprehend the underlying neurobiology of prenatal exposure to SSRIs and depressive symptoms, studies that are focused on the potential developmental plasticity from childhood to adolescence are required.

Studying maternal medication use and offspring outcomes raises a specific methodological challenge: confounding by indication. Confounding by indication may occur if the prescription of antidepressants is related to the symptomatology and perceived risks of pregnant women, i.e., there may be differences in depressive symptom levels and other characteristics between SSRI-using and nonusing women. We addressed this by adjusting for multiple sociodemographic factors and including specific contrasting groups: 1) women who used SSRIs before pregnancy (but not during pregnancy), 2) women who experienced clinically relevant depressive symptoms during pregnancy (without SSRI use), and 3) women with a low level of or no depressive symptoms during pregnancy.

The current study investigated the prospective association of prenatal SSRI exposure and prenatal maternal depressive symptoms (without SSRI exposure) with white matter microstructure assessed from ages 7 to 15 years. We hypothesized that children prenatally exposed to SSRIs and/or depressive symptoms would demonstrate lower structural connectivity (represented by lower FA and higher MD values), particularly in the corticolimbic white matter, than nonexposed control participants. We also hypothesized that structural connectivity would remain lower over time from childhood to adolescence. Furthermore, we expected consistently lower connectivity in SSRI-exposed children than in children exposed to prenatal maternal depressive symptoms.

## METHODS AND MATERIALS

### Setting and Participants

This study was conducted in the Generation R Study, a large population-based cohort in Rotterdam, the Netherlands, that follows children from fetal life to adolescence. Recruitment details are provided in the Supplemental Methods. In summary, mothers who participated in the study while pregnant ($n$ = 8756) were eligible for this study. After exclusions, the final sample comprised $n$ = 2978 mother-child pairs with 4552 scans (Figure S1). Table S1 shows the number of DTI scans in each neuroimaging wave. The Medical Ethics Committee of Erasmus Medical Centre, Rotterdam, approved the study. Written informed assent/consent was obtained from all participants.

### Prenatal SSRI Use and Depressive Symptoms

Information was obtained from self-report questionnaires and pharmacy prescriptions to optimally assess SSRI use during pregnancy. Throughout the first trimester, mothers were asked whether they had used medications during the preceding 6 months. During the second and third trimesters, we asked which medications were used during the previous 3 months. We assessed any SSRI intake and timing using these questionnaires (before or during pregnancy).

Information on maternal psychopathology was obtained during pregnancy (20 weeks of gestation) and the postnatal period (ages 2 months and 6 months) with the Brief Symptom Inventory, a validated self-report questionnaire containing 53 items. The 6-item depression scale of the Brief Symptom Inventory was used (Cronbach's $\alpha$ at 3 assessments ranged from 0.82 to 0.88). A weighted score for the depressive symptom scale (6 items, each ranging from 0 to 4 points) was generated by adding the item scores and dividing by the number of completed items. According to Dutch normative data, mothers with a score higher than 0.75 had clinically relevant depressive symptoms (see Supplemental Methods) (33).

Based on the above-described information, pregnant mothers were classified into 4 groups: 1) reference group ($n$ = 2640): women who did not use SSRIs and had low scores on measures of depressive symptoms at 20 weeks of gestation; 2) prenatal SSRI exposure ($n$ = 37): women who used SSRIs during pregnancy with and without depressive symptoms at 20 weeks of gestation; 3) prenatal depression exposure ($n$ = 229): women with clinically significant depressive symptoms as assessed at 20 weeks of gestation without any SSRI use before or during pregnancy; and 4) SSRI use before pregnancy ($n$ = 72): women who used SSRIs prior to pregnancy, regardless of the presence or absence of clinically relevant depressive symptoms at 20 weeks of gestation.

By using an active comparators study design, we aimed to isolate the effects of in utero exposures (SSRI and maternal depressive symptoms) while accounting for potential confounding factors, including the presence of prenatal maternal depressive symptoms. The active comparator design implicitly conditions the analysis on the indication and its severity, thus reducing the risk of bias arising from unmeasured confounders related to disease severity (34,35).

While our primary focus is on elucidating the consequences of in utero exposures, it is also evident that postnatal manifestations of depressive symptoms may influence the neurodevelopment of offspring. Postnatal depression is on the path connecting prenatal depression with the later outcome of interests, but adjusting for this mediator constitutes overadjustment and can introduce collider bias (36–38). For this reason, we selected the group of women with clinically relevant postnatal depressive symptoms only without any SSRI use ($n$ = 66) as an additional exposure group in supplementary analyses only. In these analyses, we adjusted for prenatal depressive

symptoms and maternal SSRI use to examine the associations between postnatal depressive symptoms and offspring white matter microstructures (Table S4; Figure S9).

### Image Acquisition and Processing

Participants were invited for 3 waves of magnetic resonance imaging (MRI) scanning, referred to as T1, T2, and T3. Two scanners were used to acquire neuroimaging data. At T1, diffusion MRI scans were acquired on a 3T GE Discovery MR750 MRI System (General Electric). At T2 and T3, diffusion MRI scans were collected using a study-dedicated 3T GE Discovery MR750w MRI System. For both scanners, an 8-channel receive-only head coil was used (see Supplemental Methods).

The FMRIB Software Library in FSL was used to preprocess the DTI images (version 6.0.2) (39). Nonbrain tissue was removed, eddy-current artifacts were corrected, and volume realignment for basic head motion translations and rotations was performed (40). The diffusion tensor was fitted at each voxel using a weighted least squares approach. Then, commonly used scalar metrics were derived (e.g., FA, MD). The automated FSL plugin AutoPtx was used to construct probabilistic white matter fiber tractography of each participant's scans by defining connection distributions for several large fiber bundles (see Supplemental Methods) (41,42). The quality of raw and processed diffusion images was evaluated using a combination of manual and automated methods (42). Details about the quality assurance protocol are available in the Supplemental Methods.

### Covariates

Based on the literature (21,23,24,43), several variables were selected as potential covariates: maternal age at intake, national origin, education level, marital status, substance use (tobacco, cannabis, alcohol), benzodiazepine usage during pregnancy, monthly household income, and child age at neuroimaging and sex (see Supplemental Methods).

### Statistical Analyses

For descriptive purposes, means of continuous variables and proportions (percentages) of categorical variables are presented.

To minimize multiple testing, we applied hierarchical analyses with primary models focusing on whole-brain FA and MD. In the second tier, tract-specific measures (uncinate fasciculus, cingulum bundle, superior longitudinal fasciculus, inferior longitudinal fasciculus, corticospinal tract, forceps minor, forceps major) were included to investigate how individual tracts contribute to the observed global associations.

The relationship between prenatal SSRI exposure, depressive symptoms, and the primary repeated measures of white matter microstructure from ages 7 to 15 years was examined with linear mixed-effects models. To account for repeated observations within individuals, we introduced exposure variables and covariates as fixed effects along with a random intercept and individual-specific slopes. The main effects and interaction terms for the effects of child age on brain outcomes (FA or MD change over time; interaction of age and group) were included. To account for MRI scanner differences, a random-effect term was included in the model. To facilitate interpretation of intercept differences, child age (~7 years) was centered at the sample's baseline age (see Supplemental Methods). All models were adjusted for child and maternal variables. We also explored interaction by child sex. In sensitivity analyses, we tested whether maternal depressive symptom severity during pregnancy confounded the associations. Toward this aim, the association between maternal depressive symptoms (continuous) and offspring whole-brain and tract-specific FA was examined continuously ($n$ = 109 with 155 scans, SSRI-exposed children were excluded). In addition, among children who underwent more than 2 MRI scans ($n$ = 1008 with 2536), the association between prenatal maternal depressive symptoms (continuous) and offspring whole-brain and tract-specific FA was re-examined (see Supplemental Methods).

To evaluate selection, we compared the characteristics of the study population ($n$ = 2978) with the total Generation R population at baseline ($n$ = 8756). We used the inverse probability of attrition weighting model to account for possible selection bias in sensitivity analyses (see Supplemental Methods) (44,45). To determine potentially influential observations, we performed an additional analysis to detect influential data (see Supplemental Methods) (46).

A false discovery rate correction (FDR) (Benjamini Hochberg) (47) was applied to control for type I errors for each hierarchical set of analyses separately (i.e., whole-brain scalar [whole-brain, 2 comparisons (FA and MD)] and tract-specific scalar [7 comparisons (FA and MD)]). Statistical significance was set at $\alpha < 0.05$ (2-sided). Missing covariate data were imputed using multivariate imputation by chained equations with 25 imputations; determinants and outcomes were not imputed. All analyses were conducted with R statistical software version 4.1.2 (see Supplemental Methods).

## RESULTS

### Descriptive Information

The demographic characteristics of the study population are shown in Table 1. Women who used SSRIs during pregnancy had lower incomes on average and were more likely to use tobacco and cannabis than the reference group. Women with clinically significant depressive symptoms were younger, more commonly of non-Dutch national origin, more likely to have lower education levels, more likely to be single mothers, and more likely to use tobacco or cannabis. Women who used SSRIs before becoming pregnant were more likely to use tobacco and had lower incomes than the reference group. Mean depressive symptoms scores in the reference, prenatal SSRI exposure, prenatal depression exposure, and SSRI use before pregnancy groups were 0.10, 0.91, 1.41, and 0.17, respectively (Table 1). Table S4 provides additional information on the characteristics of women with clinically relevant postnatal depressive symptoms. All exposure groups exhibited higher levels of postnatal depressive symptoms when compared to the reference group. Results of the nonresponse analysis are reported in the Supplemental Methods.

**Table 1. Demographic Characteristics of the Study Sample**[a]

| Characteristic | Reference, *n* = 2640 | Prenatal SSRI Exposure, *n* = 37 | Prenatal Depression Exposure, *n* = 229 | SSRI Use Before Pregnancy, *n* = 72 |
|---|---|---|---|---|
| Maternal Age at Intake, Years | 31.1 (4.4) | 32.5 (4.8) | 28.3 (5.7) | 31.1 (5.1) |
| Maternal National Origin | | | | |
| Dutch | 1681 (63.7%) | 24 (64.9%) | 59 (25.8%) | 47 (65.3%) |
| Non-Dutch Western | 234 (9%) | 4 (10.8%) | 17 (7.4%) | 3 (4.2%) |
| Non-Dutch Non-Western | 725 (27.3%) | 9 (24.3%) | 153 (66.8%) | 22 (30.6%) |
| Marital Status, With Partner | 2404 (91.1%) | 32 (86.5%) | 153 (66.8%) | 65 (90.3%) |
| Maternal Education Level | | | | |
| Primary or lower | 134 (5.1%) | 4 (10.8%) | 41 (17.9%) | 2 (2.8%) |
| Secondary | 1042 (39.4%) | 15 (40.5%) | 138 (60.3%) | 37 (51.4%) |
| Higher | 1464 (55.5%) | 18 (48.6%) | 50 (21.8%) | 33 (45.8%) |
| Maternal Monthly Household Income, €/mo | | | | |
| <1200 | 307 (11.5%) | 8 (21.6%) | 107 (46.7%) | 13 (18.1%) |
| 1200–2000 | 359 (13.6%) | 7 (18.9%) | 48 (21%) | 10 (13.9%) |
| >2000 | 1974 (74.9%) | 22 (59.5%) | 74 (32.3%) | 49 (68.1%) |
| Maternal Tobacco Use | | | | |
| Never during pregnancy | 2099 (79.5%) | 23 (62.2%) | 146 (63.8%) | 44 (61.1%) |
| Until pregnancy was known | 225 (8.5%) | 4 (10.8%) | 13 (5.7%) | 11 (15.3%) |
| Continued during pregnancy | 316 (12%) | 10 (27%) | 70 (30.6%) | 17 (23.6%) |
| Maternal Cannabis Use | | | | |
| Never during pregnancy | 2500 (94.7%) | 32 (86.5%) | 210 (91.7%) | 67 (93.1%) |
| Before pregnancy | 84 (3.2%) | 1 (2.7%) | 3 (1.3%) | 1 (1.4%) |
| During pregnancy | 56 (2.1%) | 4 (10.8%) | 16 (7%) | 4 (5.6%) |
| Maternal Alcohol Use | | | | |
| Never during pregnancy | 986 (37.4%) | 15 (40.5) % | 112 (48.9%) | 29 (40.3%) |
| Until pregnancy was known | 379 (14.3%) | 9 (24.3%) | 21 (9.2%) | 7 (9.7%) |
| Throughout pregnancy, occasionally | 986 (37.4%) | 9 (24.3%) | 86 (37.6%) | 28 (38.9%) |
| Throughout pregnancy, frequently | 289 (10.9%) | 4 (10.8%) | 10 (4.4%) | 8 (11.1%) |
| Maternal Use of Benzodiazepine During Pregnancy | 42 (1.6%) | 11 (29.7%) | 3 (1.3%) | 14 (19.8%) |
| Maternal GSI,[b] 20 Weeks of Gestation | 0.19 (0.2) | 0.82 (0.7) | 1.1 (0.5) | 0.31 (0.2) |
| Maternal Depressive Symptom Score[b] | | | | |
| 20 weeks of gestation | 0.10 (0.2) | 0.91 (0.6) | 1.41 (0.63) | 0.17 (0.2) |
| 2 mo postnatal, *n* = 2070 | 0.12 (0.2) | 0.61 (0.7) | 0.8 (0.8) | 0.6 (0.8) |
| 6 mo postnatal, *n* = 1847 | 0.16 (0.3) | 0.7 (0.8) | 0.83 (0.9) | 0.6 (0.9) |
| Child Sex, Male | 1250 (47%) | 19 (51.4%) | 113 (49.3%) | 34 (47.2%) |
| Child Gestational Age at Birth, Weeks | 39.9 (1.7) | 38.6 (3.1) | 39.9 (1.7) | 40.1 (1.2) |
| Child Age at Neuroimaging, Years | | | | |
| T1, *n* = 703 | 8.03 (1) | 7.3 (0.8) | 7.4 (0.8) | 7.8 (0.9) |
| T2, *n* = 2257 | 10.1 (0.6) | 10.1 (0.6) | 10.2 (0.7) | 10.2 (0.7) |
| T3, *n* = 1592 | 13.9 (0.5) | 14.1 (0.5) | 14.1 (0.6) | 13.9 (0.6) |

Values are presented as *n* (%) or mean (SD). Reference group: no SSRI use and a low score on depression symptoms during pregnancy; prenatal SSRI exposure: children exposed to SSRIs during pregnancy; prenatal depression exposure: children exposed to clinically relevant depressive symptoms during the pregnancy without any SSRI exposure; SSRI use before pregnancy: maternal SSRI use before pregnancy only.

GSI, Global Severity Index; SSRI, selective serotonin reuptake inhibitor.

[a]Pooled imputed data are shown (except for maternal depressive symptom scores).

[b]Scores range from 0 to 4, with higher scores indicating more clinically relevant psychological symptoms.

## Fractional Anisotropy

**At Age 7 Years.** First, we present the association of prenatal SSRI use and prenatal maternal depressive symptoms with whole-brain and tract-specific FA development (presented as estimated in fully adjusted models) at age 7 years (Figure 1). Prenatal exposure to SSRIs and prenatal depressive symptoms exhibited very similar associations with reduced whole-brain white matter microstructure as indicated by FA ($\beta = -0.023$, SE = 0.011, $p = .02$ and $\beta = -0.025$, SE = 0.004, $p < .001$, respectively). Subsequently, exploratory post hoc tract-specific analyses aimed at identifying regional specificity revealed that children whose mothers used SSRIs during pregnancy had lower white matter FA in the uncinate fasciculus, cingulum bundle, inferior longitudinal fasciculi, corticospinal tract, and forceps minor of the corpus callosum at age 7 years. However, only the association with the forceps minor survived adjustment for multiple testing ($\beta = -0.055$, SE = 0.021, $p = .004$) (Figure 1; Table 2).

Children who were exposed to maternal depressive symptoms during pregnancy had lower FA in the uncinate fasciculus, cingulum bundle, superior longitudinal fasciculi, inferior longitudinal fasciculi, corticospinal tract, and forceps minor of the corpus callosum at age 7 years than unexposed control participants. These findings closely resemble those obtained for children who were prenatally exposed to SSRI. However, all these associations remained significant after multiple testing adjustments with the exception of FA in the cingulum (Figure 1; Table 2). This observation may be attributed to the larger number of children in this group compared to those with intrauterine exposure to SSRI. No associations were found between SSRI use before pregnancy and the development of whole-brain or tract-specific FA (Figure 1; Table 2). In sensitivity analyses, no associations were identified between postnatal depressive symptoms alone and whole-brain or tract-specific FA (Figure S6). No evidence of any interaction by child sex was found in these associations.

**Follow-up (Ages 7–15 Years).** Next, we present the longitudinal associations, i.e., the developmental trajectories of white matter FA from ages 7 to 15 years. Spider charts were used at different ages to depict the estimated FA differences (%) in each group compared to the reference (Figure 2). The magnitude of the estimated differences in whole-brain FA of children who were exposed in utero to both SSRI and depressive symptoms (each compared to the unexposed reference group) was age dependent. The difference in the whole-brain FA value between those who were exposed to depression and the reference group decreased from −2.5% at age 7 to +0.5% at age 15 (age-by-group interaction $\beta = 0.001$, SE = 0.000, $p < .001$) (Figure 2; Table 2). Catch-up growth in the whole-brain FA is formally demonstrated by the significant positive age-by-group interactions in children who were prenatally exposed to depressive symptoms.

Overall, the tract-specific FA differences between SSRI-exposed children and the reference group also decreased over time, but none of these group-by-age interactions reached statistical significance (Figure 2; Table 2). Among children exposed to intrauterine depressive symptoms, white matter microstructure in multiple tracts (i.e., uncinate fasciculus, cingulum bundle, superior longitudinal fasciculi, inferior

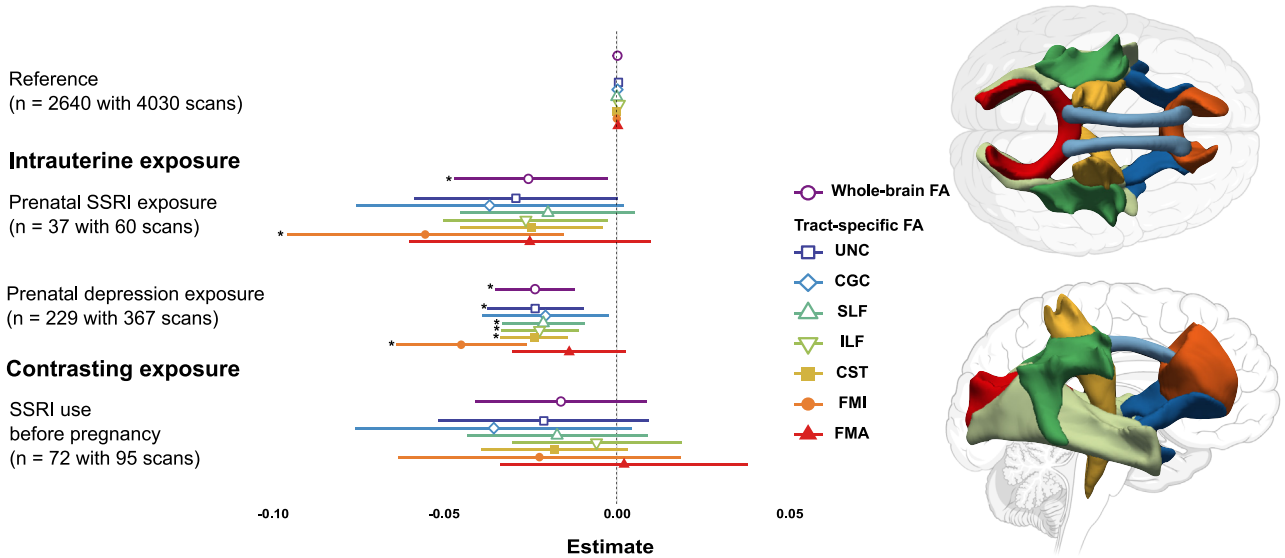


**Figure 1.** Associations between maternal selective serotonin reuptake inhibitor (SSRI) use and prenatal depressive symptoms and offspring whole-brain and tract-specific fractional anisotropy (FA) at age 7 years. Estimates are derived from fully adjusted models accounting for child sex and age at the neuroimaging assessment, maternal age at intake, maternal ethnicity, marital status, maternal education level, maternal substance use (tobacco, cannabis, alcohol), benzodiazepine use during pregnancy, and monthly household income. Weighted FA values were averaged across hemispheres for 5 bilateral tracts (uncinate [UNC], cingulum [CGC], superior longitudinal fasciculus [SLF], inferior longitudinal fasciculus [ILF], and corticospinal tract [CST]). The baseline age-centered intercept gives the predicted whole-brain and tract-specific FA at 7 years. Axial (upper) and sagittal (lower) views of the white matter tracts are depicted on the right panel. *Indicates significant associations after false discovery rate correction for multiple testing for whole-brain and tract-specific measures of white matter microstructures. FMI, forceps minor; FMA, forceps major.

**Table 2. Association of SSRI Use and Prenatal Maternal Depressive Symptoms With Offspring Whole-Brain and Tract-Specific Fractional Anisotropy**

| | Estimate (SE) | *p* Value | Estimate (SE) | *p* Value | Estimate (SE) | *p* Value | Estimate (SE) | *p* Value |
|---|---|---|---|---|---|---|---|---|
| Main Effect | Whole Brain | | Uncinate | | Cingulum | | Superior Longitudinal Fasciculi | |
| Intercept | 0.445 (0.004) | <.001[a] | 0.394 (0.005) | <.001[a] | 0.387 (0.007) | <.001[a] | 0.400 (0.004) | <.001[a] |
| Age | 0.006 (0.000) | <.001[a] | 0.006 (0.000) | <.001[a] | 0.012 (0.000) | <.001[a] | 0.006 (0.000) | <.001[a] |
| Prenatal SSRI Exposure | | | | | | | | |
| Group | −0.023 (0.011) | .02[a] | −0.030 (0.015) | .04 | −0.041 (0.019) | .05 | −0.018 (0.012) | .11 |
| Group-by-age | 0.001 (0.001) | .12 | 0.002 (0.001) | .12 | 0.001 (0.001) | .31 | 0.001 (0.001) | .19 |
| Prenatal Depression Exposure | | | | | | | | |
| Group | −0.025 (0.004) | <.001[a] | −0.024 (0.007) | <.001[a] | −0.021 (0.009) | .01 | −0.022 (0.006) | <.001[a] |
| Group-by-age | 0.001 (0.000) | <.001[a] | 0.001 (0.000) | .003[a] | 0.001 (0.000) | .02 | 0.001 (0.000) | .003[a] |
| SSRI Use Before Pregnancy | | | | | | | | |
| Group | −0.018 (0.011) | .08 | −0.019 (0.013) | .14 | −0.033 (0.018) | .05 | −0.017 (0.011) | .10 |
| Group-by-age | 0.001 (0.001) | .10 | 0.001 (0.001) | .15 | 0.002 (0.001) | .13 | 0.001 (0.001) | .12 |
| | Inferior Longitudinal Fasciculi | | Corticospinal Tracts | | Forceps Minor | | Forceps Major | |
| Intercept | 0.408 (0.004) | <.001[a] | 0.549 (0.003) | <.001[a] | 0.527 (0.006) | <.001[a] | 0.558 (0.006) | <.001[a] |
| Age | 0.007 (0.000) | <.001[a] | 0.003 (0.000) | < .001[a] | 0.008 (0.000) | <.001[a] | 0.008 (0.000) | <.001[a] |
| Prenatal SSRI Exposure | | | | | | | | |
| Group | −0.026 (0.012) | .02 | −0.024 (0.010) | .02 | −0.055 (0.021) | .004[a] | −0.025 (0.016) | .15 |
| Group-by-age | 0.002 (0.001) | .04 | 0.001 (0.000) | .10 | 0.003 (0.001) | .05 | 0.001 (0.001) | .25 |
| Prenatal Depression Exposure | | | | | | | | |
| Group | −0.023 (0.005) | <.001[a] | −0.024 (0.004) | <.001[a] | −0.044 (0.009) | <.001[a] | −0.014 (0.008) | .06 |
| Group-by-age | 0.001 (0.000) | <.001[a] | 0.001 (0.000) | <.001[a] | 0.003 (0.000) | <.001[a] | 0.001 (0.000) | .16 |
| SSRI Use Before Pregnancy | | | | | | | | |
| Group | −0.012 (0.011) | .20 | −0.021 (0.010) | .03 | −0.022 (0.018) | .19 | −0.006 (0.001) | .70 |
| Group-by-age | 0.001 (0.000) | .23 | 0.002 (0.000) | .02 | 0.001 (0.001) | .28 | 0.003 (0.001) | .57 |

Linear mixed-effect models were used to test the associations of maternal SSRI use and prenatal maternal depressive symptoms exposure and repeatedly assessed FA from ages 7–15 years. Effect estimates including the main effect and interaction effect (β) (FA change; interaction of age × group), as well as SE and *p* values are shown. The main effect estimates the difference in FA between the exposure groups vs. the reference. All models were adjusted for child sex and age at the neuroimaging assessment, maternal age at intake, maternal ethnicity, marital status, maternal education level, maternal substance use (tobacco, cannabis, alcohol), benzodiazepine use during pregnancy and monthly household income. FA of left and right tracts were averaged across hemispheres, except for the forceps minor and major as these are not bilateral tracts. The baseline age-centered intercept estimated the predicted whole-brain and tract-specific FA at 7 years.

FA, fractional anisotropy; SSRI, selective serotonin reuptake inhibitor.

[a]Indicates significant associations after false discovery rate correction for multiple testing for whole-brain tract-specific measures of white matter microstructures.

longitudinal fasciculi, corticospinal tract, and forceps minor) showed a faster FA increase with age (Figure 2). The positive age-by-group interactions shown in Table 2 illustrate the catch-up growth in these tract-specific scalars. Children prenatally exposed to depressive symptoms demonstrated normalization of FA differences in these white matter tracts over the 8-year follow-up period (Figure 2).

Sensitivity analyses revealed that continuously modeled prenatal maternal depressive symptoms exhibited a negative association with whole-brain FA and several tract-specific scalars at age 7 years (Figure S3). Furthermore, more maternal depressive symptoms were associated with a faster whole-brain FA increase during the follow-up period (age-by-depressive symptoms score interaction β = 0.001, SE = 0.000, $p < .001$) (Figure S4).

### Mean Diffusivity

There were no associations between prenatal SSRI use, prenatal and postnatal exposure to maternal depressive symptoms, and whole-brain MD in children. While some associations were observed in tract-specific models in MD, these did not survive multiple testing adjustments. Further details of the tract-specific analyses can be found in the Supplement (Figures S2 and S7; Table S3).

## DISCUSSION

In this prospective population-based study spanning from fetal life to adolescence, prenatal exposure to SSRIs and depressive symptoms were associated with lower whole-brain FA and lower FA in the forceps minor of the corpus callosum in offspring at age 7 years. In addition, higher levels of prenatal depression were associated with lower FA in the uncinate fasciculus, cingulum bundle, superior and inferior longitudinal fasciculi, and corticospinal tracts at this age. During adolescence, FA differences between children who were exposed to maternal depression in utero and those who were unexposed attenuated, suggesting potential catch-up growth.

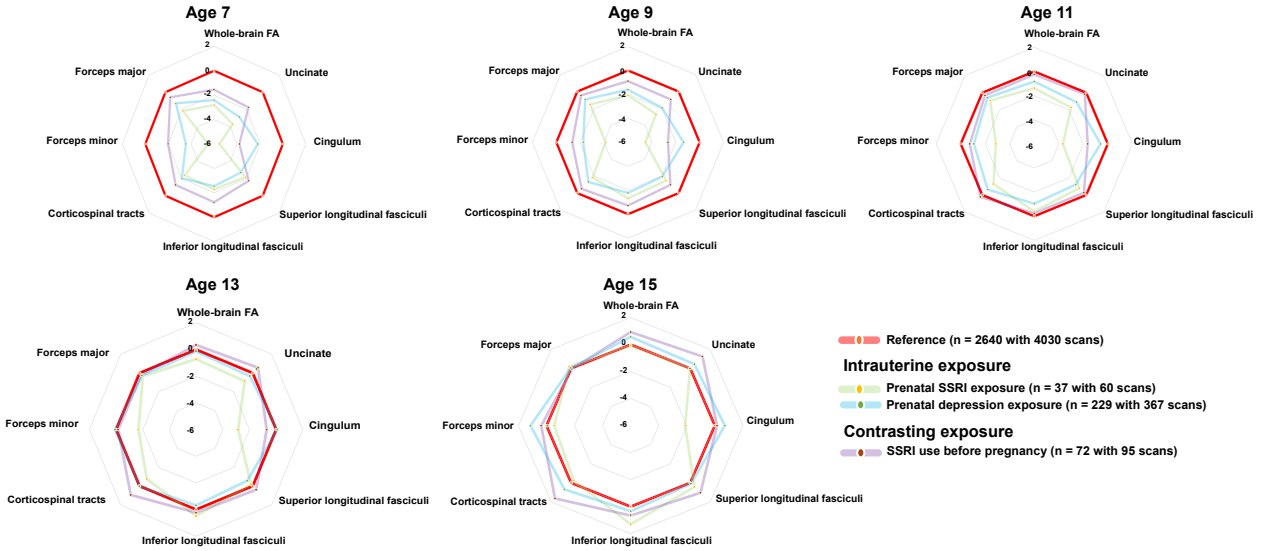


**Figure 2.** Estimated relative differences among offspring ages 7 to 15 years exposed to selective serotonin reuptake inhibitors (SSRIs) and prenatal depressive symptoms in whole-brain and tract-specific fractional anisotropy (FA). Spider charts display the estimated relative differences in whole-brain and tract-specific FA for each exposure group compared to the reference (red). These differences range from −6% to +2%. Offspring ages displayed are 7, 9, 11, 13, and 15 years. All models were adjusted for child sex and age at the neuroimaging assessment, maternal age at intake, maternal ethnicity, marital status, maternal education level, maternal substance use (tobacco, cannabis, alcohol), benzodiazepine use during pregnancy, and monthly household income. Developmental slopes for whole-brain and tract-specific FA for each exposure are shown in Figure S5.

The relationship of prenatal exposure to SSRIs and maternal depression with white matter development is unclear. Some cross-sectional studies have indicated lower FA across white matter fiber bundles in those prenatally exposed to SSRIs, while others have reported increased amygdala connectivity and localized corpus callosum alterations (20,21,25). In infants, maternal depressive symptoms during pregnancy have been associated with lower white matter diffusivity in the prefrontal, middle, and superior-parietal areas (30). To our knowledge, no prior study of prenatal SSRI or depression exposure has examined white matter development with repeated assessments during childhood or adolescence. The findings of the current study go beyond previous studies by describing trajectories that extend into adolescence. While children exposed to depressive symptoms in utero exhibited widespread lower FA at 7 years of age, by age 15 years, these children demonstrated FA values similar to those of unexposed children. While similar catch-up growth trends were observed in children exposed to SSRIs during pregnancy, the results were not statistically significant, likely due to the limited sample size. It is important to note that there was no observed association of SSRI exposure over and beyond that of depressive symptoms during pregnancy at any age in this study (ages 7–15 years). Our findings revealed no significant association of SSRI use before pregnancy with white matter microstructures. We cannot rule out the possibility that women who discontinued SSRI use before pregnancy have different characteristics or had reasons for discontinuation that could have affected the outcomes. Exposure to postnatal depression showed no significant association with white matter development during the observed period. Therefore, the association of prenatal depression with white matter development in midchildhood may reflect intrauterine mechanisms. Through the comparison of these distinct groups, we have taken a preliminary step in addressing the issue of confounding by indication. Importantly, the results of this study, contrary to our initial hypothesis, suggest that catch-up growth in white matter microstructure occurs in children with prenatal exposure to maternal depression and that adolescence may be a period when some early-life vulnerabilities weaken.

The current study revealed that neurodevelopmental changes in children exposed to maternal depressive symptoms may be compensated for during postnatal brain development (48). The phenomenon of catch-up growth in children exposed to prenatal depressive symptoms is multifaceted and can be elucidated through various processes. It has been proposed that catch-up growth observed in white matter tracts following early negative experiences such as maternal depression may represent an accelerated maturation period that compensates for slower early growth. This acceleration may come at the cost of reduced brain plasticity, which is essential for more prolonged structural brain development and functional network segregation (49). A protracted course of brain development has been associated with better cognitive abilities (50,51). An alternative explanation for the observed catch-up growth of white matter tracts following prenatal exposure to depressive symptoms is that it reflects brain plasticity and thus a return to more optimal brain development. This suggests that the brain possesses the innate capability to compensate for adverse experiences, enabling better adaptation and ultimately leading to improved long-term outcomes. Some have proposed that brain plasticity plays a pivotal role by facilitating the reorganization and rewiring of neural connections to mitigate the effects of early-life adversities (49,52,53).

The scarcity of human longitudinal studies that have explored the relationship between early-life exposures and developmental changes in myelination hinders our understanding of the molecular and cellular mechanisms that underlie the observed catch-up growth. While genetics contribute to the establishment of the initial white matter structure during the intrauterine period, the environment profoundly influences the development of dendritic complexity, synaptic connections, and myelination during the early stages of life (54). During the postnatal period, environmental experiences play a vital role in shaping brain plasticity. This plasticity may be essential for recovery from early-life adversities, particularly during the transition from childhood to adolescence (48,49,53). For example, a study on institutionally reared children showed that severe neglect in early-life compromised widespread white matter microstructure (55). However, when these children were removed from adverse conditions and placed into high-quality foster care, more normative white matter development was observed. These findings underscore the potential of early intervention and a supportive environment in mitigating the negative effects of early-life neglect on white matter microstructure. In our study, lower brain connectivity in offspring during early childhood may be attributed to prenatal maternal depression. Throughout the life course, there is a possibility that the initial adverse outcomes may be attenuated or diluted by time, although this remains speculative. Changes in FA without corresponding changes in MD could suggest that alterations in white matter microstructure are primarily related to shifts in fiber organization and directionality rather than changes in overall water diffusion (56,57). This suggests that prenatal exposure to maternal depressive symptoms may be linked to the particular structural composition of white matter tracts. To gain a deeper understanding of how postnatal factors independently and jointly shape neurodevelopment, additional longitudinal research is essential (48,54).

Several limitations of the current study must be discussed. First, because of the limited sample size of women using SSRIs, we were unable to compare specific SSRI types and explore the trimester-specific role of SSRIs. These findings must be interpreted cautiously because some of the results were based on small groups. Second, in an observational study of the potential long-term side effects of medications, it is challenging to rule out confounding by indication. Although we included multiple comparison groups to test the specificity of the observed relationship, we cannot completely rule out confounding by indication. Third, postnatal experiences during early years have the potential to significantly influence brain connectivity and may play a crucial role in moderating the impact of prenatal factors on brain development. Although child brain structure has been linked to various behavioral and cognitive functions in the general population (58), the functional implications of the reported variations have yet to be explored. Future research is required to examine long-term behavioral and cognitive outcomes associated with these white matter trajectories. In addition, the absence of neonatal MRI data limits our ability to explore earlier developmental periods comprehensively. Fourth, although the Brief Symptom Inventory is a valuable general psychopathology scale that is suitable for use in large-scale epidemiological studies, it is not among the most widely used tools for assessing prenatal and postnatal depressive symptoms. Lastly, the imaging data were acquired using 2 MRI scanners, which may introduce variability (e.g., noise and bias in the estimation of white matter scalars) when interpreting results longitudinally. Nevertheless, acquisition and data processing were performed as similarly as possible (e.g., gradient table, head coil), and we accounted for potential scanner effects (i.e., random effect term). Because this is an observational study, we cannot infer causality from the findings.

## Conclusions

This study showed that early deviations from typical white matter developmental trajectories may have normalized later in children who were exposed to prenatal depressive symptoms than they did in the reference group. A lower FA in the uncinate fasciculus, cingulum bundle, superior and inferior longitudinal fasciculi, corticospinal tract, and forceps minor at age 7 years with catch-up growth of the white matter microstructure was observed from late childhood to adolescence. Importantly, the findings in specific exposure groups (exposure to prenatal SSRIs and depressive symptoms) suggest that the current observations can be explained best by depressive symptomatology rather than SSRI use itself. Although exposure to prenatal maternal depression was largely no longer associated with brain development at age 15 years, follow-up studies are needed to fully understand the ongoing developmental trajectory of the brain and whether catch-up growth may continue beyond this age.

## ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by Marie Skłodowska-Curie Actions Innovative Training Network program (Serotonin and BEYOND, Grant agreement No. 953327 [to HT and HEM]); Stichting Volksbond Rotterdam (to HEM); the Netherlands Organization for Scientific Research Aspasia (Grant No. 015.016.056 [to HEM]), and the European Union's Horizon 2020 Research and Innovation Program (HappyMums, Grant Agreement No. 101057390 [to HEM]); and the Netherlands Organisation for Health Research and Development (ZonMw Vici project No. 016.VICI.170.200 [to HT]). Neuroimaging, image analysis, and informatics were supported by Grant No. S18-20 from the Sophia Foundation (to RLM). High-performance computing for image analysis was provided by the Dutch Organization for Scientific Research (NWO 2021.042, "Snellius"; https://www.surf.nl/). The general design of the Generation R Study is made possible by financial support from Erasmus University Medical Center; Erasmus University Rotterdam; the Netherlands Organization for Health Research and Development; the Netherlands Organization for Scientific Research; the Ministry of Health, Welfare and Sport; and the Ministry of Youth and Families. The authors sincerely acknowledge the contributions of the participating children, parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Aug 14, 2023; revised Oct 25, 2023; accepted Oct 26, 2023.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2023.10.009.

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