RESEARCH ARTICLE OPEN ACCESS

Multiple Sclerosis Relapse Treatment During Pregnancy and Offspring Functional and Structural Neurodevelopment

A Cross-Sectional Study

Valeska Kozik,[1,*] Michelle Dreiling,[1,2,*] Denise Müller,[1] Oliver Tiedge,[3] Ruth Schneider,[4] Sandra Thiel,[4] Barbara Bellenberg,[5] Britta Krieger,[5] Carsten Lukas,[5] Hans-Joachim Mentzel,[6] Christian Gaser,[1,7,8] Kerstin Hellwig,[4] Matthias Schwab,[1] and Florian Rakers[1]

Correspondence
Dr. Rakers
florian.rakers@med.uni-jena.de

Neurology® 2025;105:e214217. doi:10.1212/WNL.0000000000214217

Abstract

Background and Objectives

High-dose methylprednisolone (MP) is the global standard for treating pregnancy-associated relapses in multiple sclerosis (MS). Given that glucocorticoids cross the placenta and may interfere with fetal brain development, concerns remain about their long-term safety. This study assessed whether in utero MP exposure as part of MS relapse therapy affects neurodevelopment in school-aged children.

Methods

In this cross-sectional, 2-center study, term-born children with prenatal exposure to MP due to maternal MS relapse treatment were compared with a nonexposed reference group of children, all born to mothers with MS. Participants were primarily identified using the German MS and Pregnancy Registry and assessed at tertiary MS centers. The primary outcome was global cognitive ability, measured using a standardized intelligence test. Secondary outcomes included attention, behavior, motor performance, and electrocortical activity at rest. Structural brain development was assessed using high-resolution MRI, including voxel-based and surface-based morphometry. Deviations from chronological brain age were quantified using a machine learning–based framework. Statistical associations were examined using linear regression models.

Results

The MP-exposed group (n = 30; mean age 9.6 years; 37% female) and the reference group (n = 30; mean age 10.0 years; 40% female) were comparable with respect to demographic and perinatal characteristics. The median cumulative MP dose was 5 g (Q1–Q3: 3–7.5), predominantly administered during the second trimester. Global IQ did not differ between groups (MP: 103.0; 95% CI: 99.2–106.8 vs reference: 101.5; 95% CI: 97.6–105.3). After correction for multiple comparisons, no group differences emerged in secondary neuropsychological outcomes or electrocortical parameters. MRI analyses revealed no differences in gray matter volume, cortical thickness, gyrification, or chronological brain age.

Discussion

In spite of theoretical concerns that MP exposure during pregnancy might lead to alterations in neurodevelopment, this was not found to be the case in this cohort, with most exposures occurring during the second trimester. However, this study was not powered to detect subtle

*These authors contributed equally to this work.

[1]Department of Neurology, Jena University Hospital, Germany; [2]Clinician Scientist Program OrganAge, Jena University Hospital, Germany; [3]NeuroZentrum Erfurt, Private Practice, Germany; [4]Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Germany; [5]Institute of Neuroradiology, St. Josef Hospital, Ruhr University Bochum, Germany; [6]Department of Diagnostic and Interventional Radiology, Jena University Hospital, Germany; [7]Department of Psychiatry and Psychotherapy, Jena University Hospital, Germany; and [8]German Center for Mental Health (DZPG), partner site Jena-Magdeburg-Halle, Germany.

The Article Processing Charge was funded by Friedrich-Schiller-Universität Jena.

Glossary

11β-HSD-2 = 11β-hydroxysteroid dehydrogenase type 2; **ADHD** = attention-deficit/hyperactivity disorder; **CPT** = Continuous Performance Test; **DMT** = disease-modifying therapy; **EMM** = estimated marginal mean; **FWHM** = full-width-at-half-maximum; **M-ABC-2** = Movement Assessment Battery for Children, Second Edition; **MP** = methylprednisolone; **mRS** = modified Rankin Scale; **MS** = multiple sclerosis; **RIAS** = Reynolds Intellectual Assessment Scales; **RUB** = Ruhr University Bochum/St. Josef Hospital; **SBM** = surface-based morphometry; **SDQ** = Strengths and Difficulties Questionnaire; **SEF** = spectral edge frequency; **SES** = socioeconomic status; **UKJ** = Jena University Hospital; **VBM** = voxel-based morphometry.

associations in secondary analyses or to draw definitive conclusions regarding potential dose-response relationships. Given the remaining uncertainties, MP should be used with caution at the lowest effective dose until larger follow-up studies provide further clarity.

Introduction

Pregnancy in women with multiple sclerosis (MS) presents unique clinical challenges that require careful consideration of both maternal and fetal well-being. Choosing an appropriate MS therapy during pregnancy is critical because modern disease-modifying therapies (DMTs) often lack comprehensive pregnancy-related safety data, and some are known to have teratogenic effects.[1] Although growing evidence supports the continued use of certain highly effective DMTs during pregnancy, such as natalizumab,[2,3] it remains a common clinical practice to discontinue DMTs around conception or to switch to less effective but pregnancy-approved agents, such as glatiramer acetate or interferon β.[3,4] Although this approach reduces fetal risk, it can increase the likelihood of pregnancy-associated relapses estimated to occur at a rate of 1% per month.[5]

To manage relapses, high-dose glucocorticoid therapy is recommended by MS guidelines and is generally considered safe for the fetus.[1,6] However, because glucocorticoids can cross the placenta, they may affect fetal brain development by promoting maturation at the expense of cell division.[7] Previous studies have shown that prenatal exposure to synthetic corticosteroids, such as betamethasone used for fetal lung maturation, can lead to long-term neurodevelopmental consequences, including a reduced IQ,[8,9] behavioral disturbances,[8-10] altered electrocortical activity,[8,10] and decreased cortical thickness.[11] Notably, the dosage of corticosteroids for treating MS relapses is up to 50-fold higher than the doses used in obstetric settings.[12]

Despite the widespread use of glucocorticoids for MS relapse management during pregnancy, no studies have investigated the long-term neurodevelopmental outcomes of children prenatally exposed to this treatment. This study aims to address this gap by evaluating neurocognitive and electrocortical outcomes, as well as neuroimaging-derived biomarkers of structural brain development in school-aged children exposed to the glucocorticoid methylprednisolone (MP) as part of maternal MS relapse therapy. Our primary hypothesis was that prenatal exposure to MP would be associated with lower IQ scores compared with a nonexposed reference group. Secondary outcomes included additional cognitive performance markers, behavior, motor development, and electrocortical markers of functional brain maturation. Structural brain development was assessed using high-resolution MRI, incorporating voxel-based morphometry (VBM) of gray matter volume, surface-based morphometry (SBM) of cortical thickness and gyrification, and deviations from biological brain aging quantified by the machine learning-based BrainAGE score.[13]

Methods

The detailed study protocol has been previously published elsewhere[12] and is briefly summarized in this study.

Research Design

A 2-center, observational, cross-sectional study in children and adolescents prenatally exposed to MP as part of maternal MS relapse therapy (MP-exposed group) vs nonexposed children of mothers with MS (reference group) was conducted. Outcome assessment was conducted at the Jena University Hospital (UKJ) and the Ruhr University Bochum/St. Josef Hospital (RUB) in Germany between October 2020 and August 2023.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval of the ethics committees of UKJ (Reference: 2020-1668-3-BO) and RUB (Reference: 21-7192 BR) and informed consent from all participants and their parents was obtained. The study protocol was registered under ClinicalTrials.gov (identifier: NCT04832269).

Recruitment Strategy

For the MS and reference group, potential participants and their mothers with an MS diagnosis were primarily identified through the German MS and Pregnancy Registry and invited through mail or e-mail. This nationwide observational cohort enrolls pregnant women with MS through physician referrals and self-enrollment; eligibility requires a self-reported MS diagnosis and ongoing pregnancy.[14] In addition, we used the clinical database of the UKJ MS center, which includes routinely collected data

on patients with MS since 2003. To ensure comparability with the MP group, children for the reference group were selected using frequency matching on sex, age (±12 months), and parental educational background. Allocation to a study center for assessment was determined by the participants' preferences. The recruitment process is illustrated in Figure 1.

Inclusion and Exclusion Criteria

Offspring aged 8–18 years whose mothers were diagnosed with MS by a specialized neurologist were eligible for participation. Inclusion in the MP group required intrauterine exposure to MP administered for the treatment of maternal MS relapse, irrespective of dosage or timing. For the reference group, the inclusion criteria were a maternal MS diagnosis received before pregnancy and no MP exposure during pregnancy. Exclusion criteria for both groups included any perinatal complications (e.g., cerebral hemorrhage, neonatal intensive care requiring mechanical ventilation) or any additional prenatal therapy with corticosteroids beyond MP. Additional exclusion criteria were maternal noxious substance use during pregnancy, severe illnesses in the children that would make examination impossible (e.g., intellectual disability), long-term medication with corticosteroids (e.g., for asthma), birth before the completion of the 34th week of pregnancy, or a birth weight below the 5th percentile.

Demographic and Clinical Baseline Data

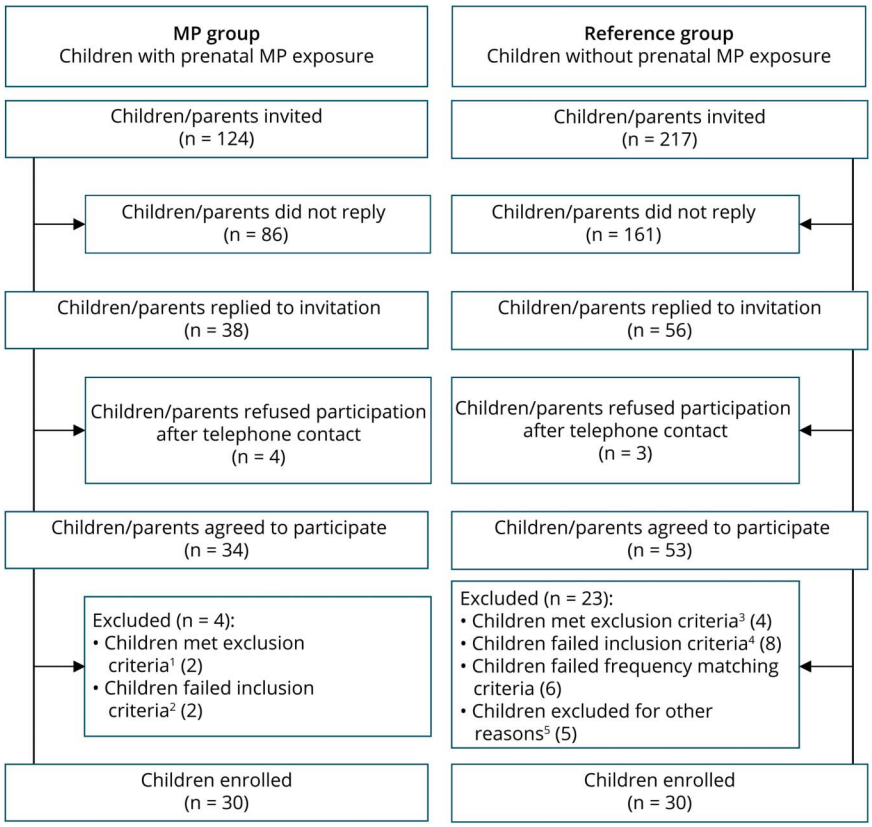
Sociodemographic variables, including socioeconomic status (SES, defined by parental education level and disposable household income) as well as pregnancy and birth data, were collected using parental questionnaires[8,10] and maternity notes, an official pregnancy-specific German health record. The characteristics of MS and MP exposure were self-reported by participants using a medical history form and verified by study staff using medical files. Owing to limited availability of Expanded Disability Status Scale data, maternal disability status was assessed using the modified Rankin Scale (mRS). Stressful life events during the past 12 months of the child's life were assessed using a German self-report questionnaire (Zürcher Life Events List[15]) because such stress could influence neuropsychological test results.

Outcomes of Interest

Functional Brain Development: Neuropsychological Outcomes and Electrocortical Activity

Neuropsychological outcome measures were obtained by a trained psychologist at approximately the same time in the morning to ensure consistency and accuracy in the assessment process. EEG recordings were conducted in the afternoon, whereas MRI assessments were performed on a separate day.

Figure 1 Flowchart of the Study Recruitment Process



[1]MP relapse treatment not confirmed (n = 1), maternal substance use during pregnancy (n = 1). [2]Child aged <8 years (n = 2). [3]Additional glucocorticoid therapy for lung maturation (n = 4). [4]MS diagnosis after pregnancy (n = 5), child aged <8 years (n = 3). [5]For example, long travel distance and scheduling difficulties. MP = methylprednisolone.

Primary Outcome

The primary outcome measure of this study was the child's global cognitive ability measured by the age-adjusted Reynolds Intellectual Assessment Scales (RIAS).[16] The RIAS comprises 2 subscales that evaluate both verbal and nonverbal intelligence, yielding a composite IQ score that reflects the child's global intellectual abilities in terms of reasoning and problem-solving. The additional memory scale indicates a child's verbal and nonverbal (working) memory capacity and is scored separately from the global IQ scale.

Secondary Neuropsychological Outcomes

Secondary clinical outcomes were the child's attentional performance (selective and sustained attention and response inhibition), as measured by the Continuous Performance Test (CPT),[17] emotional excitability determined using the respective subtest of a self-report personality questionnaire for children (PFK 9–14), [18] and attention-deficit/hyperactivity disorder (ADHD) symptoms evaluated using a parent-reported questionnaire (FBB-ADHS from DISYPS-III).[19] In addition, behavioral difficulties were determined using the parent-reported Child Behavior Checklist (CBCL/6-18R)[20] and the Strengths and Difficulties Questionnaire (SDQ).[21] Motor development was assessed using the Movement Assessment Battery for Children, Second Edition (M-ABC-2),[22] which evaluates manual dexterity, aiming and catching, and balance skills.

Electrocortical Activity

In addition to neuropsychological outcomes, functional brain development was estimated by calculating the spectral edge frequency (SEF) of continuous resting-state EEG recordings (30 minutes, eyes open) using 4 pairs of electrodes (frontal, parietal, temporal, and occipital; sample rate 128 Hz; and reference channel Cz), as described elsewhere.[8,12] The SEF, defined as the frequency below which 95% of the EEG power resides, provides an estimate of the frequency content of the EEG power spectrum generated by thalamo-cortical and cortico-cortical networks.[23] Higher SEF values have been linked to cortical maturation and increasing neurodevelopmental complexity in children.[8,10,24]

Structural Brain Development

Structural brain development was assessed using high-resolution MRI, including VBM for gray matter volume, SBM for cortical thickness and gyrification, and BrainAGE to quantify deviations from biological brain aging.

MRI Acquisition and Preprocessing

MRI data were acquired using a Siemens TIM Trio 3T MRI System (Siemens, Erlangen, Germany) at UKJ and an Achieva Philips 3T MRI System (Philips Healthcare, Best, the Netherlands) at RUB. In both centers, high-resolution structural T1-weighted images were obtained with a resolution of 1 × 1 × 1 mm^3. MRI data were processed and analyzed using the CAT12 toolbox, as detailed elsewhere.[25] For processing and analysis steps, preset parameters were used in accordance with standard protocols.[25] Processing included a 2-step quality assurance process comprising a visual inspection for artefacts and a statistical quality control for intersubject homogeneity and overall image quality, as implemented in the CAT12 toolbox.

VBM and SBM

For the VBM analysis, tissue segmentation and spatial registration were performed to classify voxels into 3 tissue types: gray matter, white matter, and CSF. Using modulated normalized gray matter maps, we tested the hypothesis of regional gray matter volume differences. These maps were smoothed with an 8-mm full-width-at-half-maximum (FWHM) Gaussian kernel to enhance the signal-to-noise ratio. An absolute masking threshold of 0.1 was applied to the VBM data.

In the SBM analysis, cortical thickness and gyrification were examined. Cortical thickness was calculated using a projection-based distance measurement from the inner to the outer cortical surface, implemented in the CAT12 toolbox.[26] Gyrification was assessed using gyrification index maps derived from the local absolute mean curvature approach,[27] averaging curvature values within a 3-mm radius around each vertex. Both measures were smoothed using a Gaussian kernel, with cortical thickness at 12 mm FWHM and gyrification at 25 mm FWHM.

Brain Age Estimation

The BrainAGE approach used in this study models healthy brain development to estimate individual brain age.[13] It has been validated in numerous neurodevelopmental studies, including those involving children and adolescents.[28] The algorithm is based on Gaussian Process Regression. In this study, we followed the established workflow,[13,29] but the model was trained on an expanded sample of 879 healthy children and adolescents aged 5–22 years (mean age: 12.3 years), using data from the NIH Pediatric MRI Data Repository (4th release). This trained algorithm was applied to the processed gray matter MRI images of the current sample to estimate each child's brain age (see above). The BrainAGE score is calculated as the difference between the estimated (biological) brain age and the chronological age. A negative score indicates a delay in brain maturation, whereas a positive score suggests accelerated maturation.

Statistical Analysis

Functional Brain Development: Neuropsychological Outcomes and Electrocortical Activity

Based on previous findings by some of the authors,[8] we initially aimed to enroll 35 children per group, ensuring a minimum data set of 30 analyzable participants per group. This design was calculated to achieve 81.5% power to detect a standardized mean IQ difference of 0.75 (2-sided $\alpha = 0.05$).

Household SES was dichotomized into "university education" and "no university education" based on the highest parental educational level. Neuropsychological test scores were age-adjusted to normative data where available and z-transformed for comparability. M-ABC-2 scores were expressed as percentile ranks, whereas SDQ scores were reported as raw values because of the lack of standardized norms. Inverted scoring was applied to ensure interpretive consistency across all measures.

Robust linear regression was used to evaluate the association between MP exposure and neuropsychological outcomes and electrocortical activity, accounting for potential outliers. MM estimation with Huber weighting function (k = 1.345) was used, and scale parameters were determined using the median absolute deviation. Initial estimates were obtained using least trimmed squares.

For adjusted group comparisons, estimated marginal means (EMM) were computed while holding covariates constant. Pairwise z-tests were applied to EMM contrasts to assess between-group differences. The effects of MP exposure were analyzed using univariable models (MP exposure only) and multivariable models adjusting for sex and SES in neuropsychological outcomes and for sex and age in electrocortical activity. Exploratory analyses investigated potential associations between cumulative MP dose, gestational timing of exposure, and outcome measures using similar modeling approaches.

All analyses were conducted using robust linear regression with inference based on 95% CIs. For adjusted group comparisons, statistical significance was determined at a threshold of $p < 0.05$. To account for multiple comparisons, the Benjamini-Hochberg procedure was applied to control the false discovery rate. Statistical testing was restricted to outcome variables. For each outcome, analyses were conducted using all available cases; no imputation was performed. All analyses were conducted using R (version 4.4.1).

Structural Brain Development

Statistical analyses were conducted using the CAT12 statistical module, applying general linear models for each morphometric method with age and sex as covariates. For VBM, total intracranial volume was additionally included as a covariate. Group differences in the BrainAGE score were evaluated using 2-tailed t tests. Thresholds were set at $p < 0.05$, with family-wise error correction for multiple comparisons.

Data Availability

Anonymized data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Sociodemographic and Clinical Baseline Data

The study included 60 children, evenly divided between the MP-exposed group (n = 30) and the reference group (n = 30) (Table 1). The mean age was comparable between groups (MP: 9.6 ± 1.7 [SD] years; reference: 10 ± 1.5 years), as was the proportion of female patients, the frequency of only children, type of school attended, or reported stress levels over the past 12 months. Parental demographics, including maternal and paternal ages and socioeconomic status, were also similar.

Pregnancy and birth outcomes were largely consistent between the groups, although the MP-exposed group had a slightly shorter gestational age at birth (mean 270.7 ± 9.9 days vs 276.8 ± 9.8 days). No major or minor congenital anomalies, including cleft palate, were observed in either group.

Regarding MS severity in the mothers, the MP-exposed group exhibited higher mRS scores both before (median = 1 [Q1–Q3: 0.25–2] vs median = 0 [Q1–Q3: 0–1]) and after pregnancy (median = 2 [Q1–Q3: 1–2] vs median = 1 [Q1–Q3: 0–2]). In addition, the use of DMT during pregnancy was more common in the MP group (41.4% vs 16.7%, Table 1).

Exposure Characteristics

In the MP-exposed group, the median cumulative dose of maternal MP exposure was 5 g (Q1–Q3: 3–7.5 g), corresponding to the median treatment duration of 5 days per pregnancy (Q1–Q3: 3–7.5 days). A single course of MP was administered in 70% (n = 21) of cases, whereas 30% (n = 9) received 2 or more courses to treat more than 1 relapse per pregnancy. MP courses were predominantly administered in the second trimester (61.5%, n = 24), followed by the third trimester (28.2%, n = 11) and the first trimester (10.3%, n = 4).

Functional Brain Development

Neuropsychological Outcomes

No difference in the primary outcome IQ was observed between the MP group and the reference group in either univariable or multivariable analyses (Figure 2, Table 2).

Multivariate analyses of secondary neuropsychological end points suggested reduced attentional performance in the MP group compared with the reference group, as indicated by higher omission error rates in the CPT (z-score; adjusted mean difference = −0.6; 95% CI: −1.1 to −0.2; unadjusted $p = 0.01$, Table 2, Figure 3). In addition, children in the MP group exhibited lower emotional excitability on a personality questionnaire (−0.6; 95% CI: −1.1 to −0.1; unadjusted $p = 0.02$, Table 2, Figure 3). However, these associations did not survive correction for multiple comparisons (adjusted $p = 0.1$ and $p = 0.13$, respectively). No other differences in neuropsychological outcome measures were observed between MP-exposed and reference children.

Exploratory analyses examining the gestational week and total cumulative dose of MP exposure revealed no associations with neuropsychological outcomes, including global IQ and its subscales (Table 3). The analysis by gestational week included 20 children; 10 were excluded because of multiple exposures across trimesters or missing retrospective

Table 1 Cohort Characteristics

	MP-exposed (n = 30)	Reference (n = 30)
Demographic and socioeconomic data		
Child		
Age, y, mean (SD)	9.6 (1.7)	10 (1.5)
Female sex, n (%)	11 (36.7)	12 (40)
Only child, n (%)	9 (30)	5 (16.7)
School type currently attending, n (%)		
Primary school	20 (66.7)	16 (55.2)
Secondary school	2 (6.7)	2 (6.7)
High school	8 (26.7)	11 (37.9)
Special needs school	0 (0)	0 (0)
Stress level last 12 mo (ZLEL), mean (SD)	−4 (4.9)	−4 (4.8)
Psychiatric disorders[a], n (%)	2 (6.7)	3 (10)
Parents		
Maternal age, y, mean (SD)	41.1 (4.4)	41 (4.6)
Paternal age, y, mean (SD)	43.8 (4.5)	44.1 (6.2)
Socioeconomic status		
University degree, at least 1 parent, n (%)	18 (60)	17 (56.7)
Household income ≥ €4,000, n (%)	19 (63.3)	14 (48.3)
Psychiatric disorders[a], at least 1 parent, n (%)	3 (10)	7 (23.3)
Pregnancy data		
Stressful life events, median (Q1–Q3)	1 (0–2.8)	0.5 (0–2.5)
Pregnancy complications		
Abortus imminens, n (%)	3 (10.3)	0 (0)
Other bleeding during pregnancy, n (%)	0 (0)	1 (3.3)
Pre-eclampsia, n (%)	7 (24.1)	12 (41.4)
Tocolytic treatment, n (%)	3 (10.3)	1 (3.3)
Birth data		
Maternal age at birth, y, mean (SD)	31.5 (3.8)	30.9 (4.4)
Cesarean section, n (%)	8 (26.7)	10 (33.3)
Gestational age at birth, d, mean (SD)	270.7 (9.9)	276.8 (9.8)
Birth weight, g, mean (SD)	3,252 (505)	3,249 (430)
Birth length, cm, mean (SD)	50.6 (2.2)	50.4 (2.5)
Head circumference, cm, mean (SD)	34.8 (1.1)	34.8 (1.3)
APGAR 10, median (Q1–Q3)	10 (10–10)	10 (10–10)
Child breast-fed, n (%)	17 (56.7)	24 (80)
MS data		
Disease course		
Relapsing-remitting, n (%)	28 (93.3)	28 (93.3)

Continued

Table 1 Cohort Characteristics *(continued)*

	MP-exposed (n = 30)	Reference (n = 30)
Secondary progressive, n (%)	2 (6.7)	2 (6.7)
mRS before pregnancy, median (Q1–Q3)	1 (0.25–2)	0 (0–1)
mRS after pregnancy, median (Q1–Q3)	2 (1–2)	1 (0–2)
Relapses (treated or untreated), median (Q1–Q3)	1 (1–2)	0 (0)
DMT (anytime during pregnancy), n (%)	12 (41.4)	5 (16.7)
Interferon β/glatiramer acetate	5 (16.3)	3 (10)
Dimethyl fumarate	0 (0)	1 (3.3)
Natalizumab	3 (10)	1 (3.3)
Immunoglobulins	3 (10)	0 (0)
Not specified	1 (3.3)	0 (0)

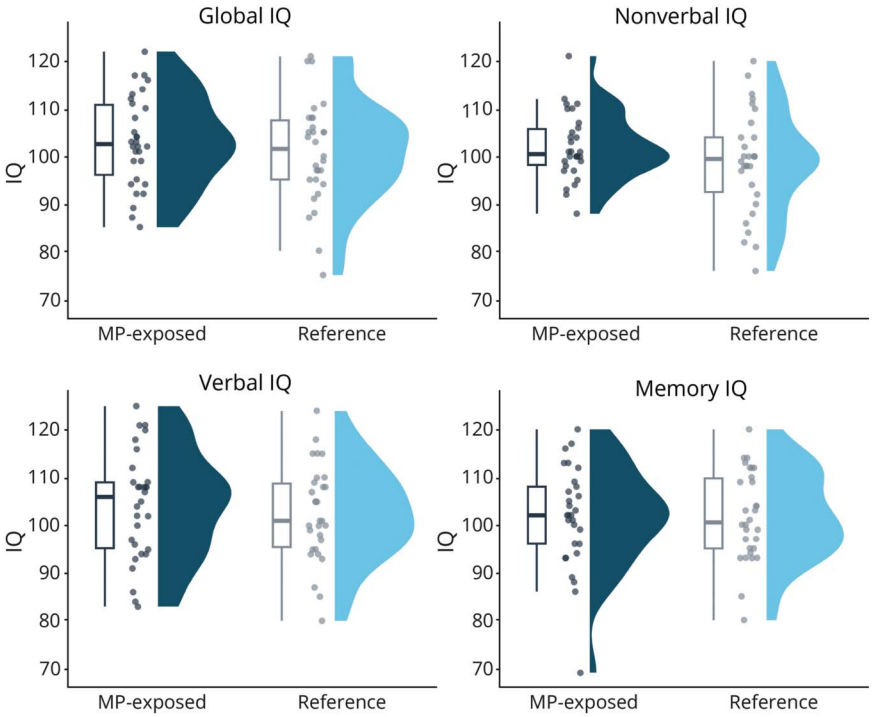
Abbreviations: APGAR 10 = APGAR score 10 minutes after birth; DMT = disease-modifying MS therapy; MP = methylprednisolone; mRS = modified Ranking Scale; MS = multiple sclerosis.
[a] Attention-deficit/hyperactivity disorder, depression, or anxiety disorder.

documentation of the exact timing. The dose-response analysis included 29 children, with 1 excluded because of insufficient data on cumulative MP dose.

Electrocortical Activity

MP-exposed children exhibited reduced electrocortical activity at frontal electrodes, as measured by SEF, compared with reference children (−1.3 Hz; 95% CI: −2.2 Hz to −0.4 Hz; unadjusted $p = 0.01$, Table 2, Figure 3). However, this difference did not remain statistically significant after correction for multiple comparisons (adjusted $p = 0.1$). No group differences were observed at other electrode positions. In addition, no associations were found between electrocortical activity and either MP dose or gestational timing of exposure (Table 3).

Figure 2 Distributions of IQ Scores



The figure presents standard boxplots with whiskers extending to 1.5 times the interquartile range. Dots represent individual IQ scores; density curves illustrate their distribution.

Table 2 Summary Statistics of Neuropsychological Outcomes and Electrocortical Activity

		Estimates						Comparisons				
		MP			Reference			MP vs reference				
Outcome	Scale	EMM	SE	95% CI	EMM	SE	95% CI	MD	SE	95% CI	*p* Value	p_{adj}
Primary outcome												
IQ												
Global IQ	IQ	103	2	99.2 to 106.8	101.5	2	97.6 to 105.3	1.6	2.7	−3.7 to 6.9	0.56	0.8
Nonverbal IQ	IQ	101.6	1.7	98.3 to 104.9	99.2	1.7	95.9 to 102.6	2.3	2.4	−2.3 to 6.9	0.32	0.58
Verbal IQ	IQ	104.1	2.1	100 to 108.1	102.8	2.1	98.7 to 107	1.2	2.9	−4.5 to 6.9	0.68	0.85
Memory IQ	IQ	102.9	1.9	99.1 to 106.7	102.7	1.9	98.9 to 106.5	0.2	2.7	−5 to 5.5	0.93	0.98
Secondary outcomes												
Motor development (M-ABC-2)	PR	47.3	5.5	36.6 to 58	47.4	5.4	36.7 to 58.1	−0.1	7.5	−14.9 to 14.7	0.99	0.99
Attention												
CPT reaction time	z	−0.1	0.2	−0.5 to 0.3	0.2	0.2	−0.3 to 0.6	−0.2	0.3	−0.8 to 0.3	0.24	0.52
CPT omission errors	z	−0.1	0.2	−0.5 to 0.2	0.5	0.2	0.2 to 0.8	−0.6	0.2	−1.1 to −0.2	0.01	0.1
CPT commission errors	z	−0.1	0.2	−0.5 to 0.3	0.2	0.2	−0.3 to 0.6	−0.2	0.3	−0.8 to 0.3	0.41	0.63
Emotional excitability	z	0	0.2	−0.4 to 0.4	0.6	0.2	0.2 to 1	−0.6	0.2	−1.1 to −0.1	0.02	0.13
ADHD symptoms												
ADHD global score	z	−0.3	0.2	−0.6 to 0.1	0.1	0.2	−0.3 to 0.4	−0.4	0.3	−0.8 to 0.1	0.11	0.34
ADHD hyperactivity	z	−0.3	0.2	−0.6 to 0.1	0	0.2	−0.4 to 0.3	−0.3	0.2	−0.8 to 0.2	0.12	0.34
ADHD inattention	z	−0.2	0.2	−0.5 to 0.2	0.1	0.2	−0.2 to 0.5	−0.4	0.3	−0.9 to 0.1	0.26	0.52
Behavioral difficulties												
CBCL global score	z	−0.7	0.2	−1.1 to −0.3	−0.5	0.2	−0.9 to −0.1	0.1	0.3	−0.4 to 0.7	0.39	0.63
CBCL internalizing	z	0.8	0.2	0.5 to 1.2	0.5	0.2	0.1 to 0.9	0.1	0.3	−0.4 to 0.7	0.16	0.4
CBCL externalizing	z	0.2	0.2	−0.2 to 0.6	0.1	0.2	−0.3 to 0.5	−0.2	0.3	−0.8 to 0.3	0.63	0.84
Strengths and difficulties (SDQ)	Raw	−8.6	1.1	−10.8 to −6.5	−8.4	1.1	−10.5 to −6.2	−0.3	1.5	−3.2 to 2.7	0.86	0.96
Electrocortical activity												
Frontal	SEF	19.7	0.4	19 to 20.4	21	0.3	20.3 to 21.6	−1.3	0.5	−2.2 to −0.4	0.01	0.1
Temporal	SEF	18.2	0.3	17.7 to 18.8	18.3	0.3	17.8 to 18.8	−0.1	0.4	−0.8 to 0.6	0.8	0.94
Parietal	SEF	21.2	0.4	20.4 to 22.1	22.2	0.4	21.3 to 23	−1	0.6	−2.1 to 0.2	0.11	0.34
Occipital	SEF	20.6	0.5	19.6 to 21.5	19.4	0.5	18.5 to 20.3	1.2	0.7	−0.1 to 2.5	0.07	0.34

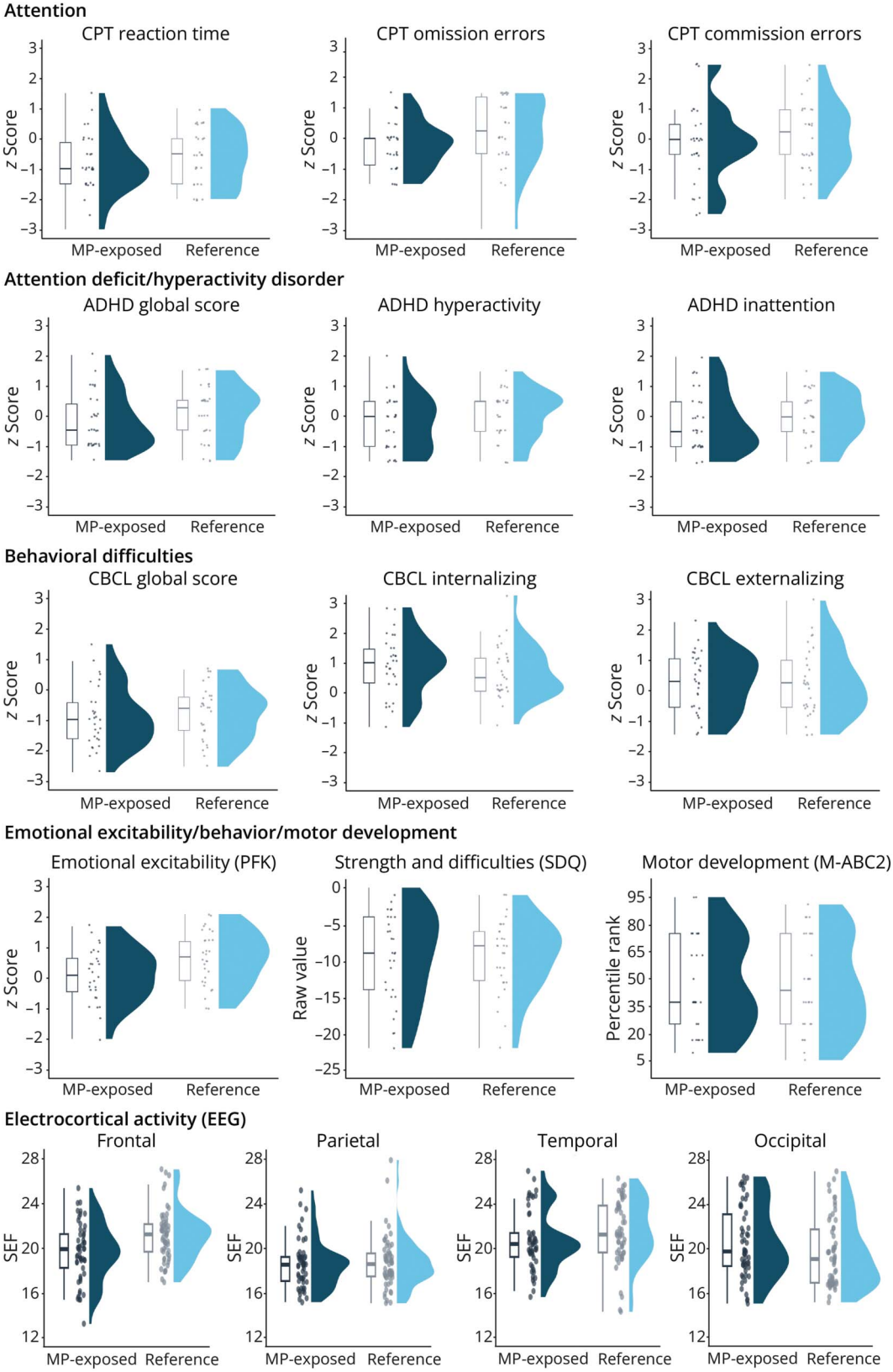
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CBCL = child behavior checklist; CPT = Continuous Performance Test; EMM = estimated marginal means; M-ABC-2 = Movement Assessment Battery for Children, Second Edition; MD = mean difference; MP = methylprednisolone; p_{adj} = *p* value after Benjamini-Hochberg correction for multiple comparisons; PFK = German personality questionnaire; PR = percentile rank; SDQ = Strengths and Difficulties Questionnaire; SE = standard error; SEF = spectral edge frequency.
Neuropsychological outcomes: Lower values denote worse performance/outcomes, results adjusted for socioeconomic background and child sex. Electrocortical activity: Results adjusted for child age and sex.

Structural Brain Development

A total of 40 MRI scans were analyzed (MP group: n = 20, reference group: n = 20). Neither VBM nor SBM analysis revealed significant group differences in gray matter volume, cortical thickness, or cortical gyrification.

We computed the BrainAGE score for the MP group (0.2 ± 1.29 years) and the reference group (−0.32 ± 1.1 years) (Figure 4), revealing that both groups' biological brain ages closely matched their chronological age, with no statistically significant differences observed.

Figure 3 Distributions of Secondary Neuropsychological and Electrocortical Outcomes



The figure presents standard boxplots with whiskers extending to 1.5 times the interquartile range. Dots represent individual scores or measures, and density curves illustrate their distribution. ADHD = attention deficit/hyperactivity disorder; CBCL = Child Behavior Checklist; CPT = Continuous Performance Test; M-ABC-2 = Movement Assessment Battery for Children, Second Edition; MP = methylprednisolone; PFK = German personality questionnaire; SDQ = Strengths and Difficulties Questionnaire; SEF = spectral edge frequency.

Table 3 Robust Linear Regression Models Assessing the Association of Cumulative MP Dosage and Gestational Timing With Neuropsychological Outcomes and Electrocortical Activity

		Cumulative dose of MP (g) (n = 29)			Gestational week of MP exposure (n = 20)		
Outcome	Scale	Regression coefficient	95% CI	Evidence of association	Regression coefficient	95% CI	Evidence of association
Primary outcome							
IQ							
Global IQ	IQ	−0.73	−1.8 to 0.34	No	−0.08	−0.63 to 0.47	No
Nonverbal IQ	IQ	−0.53	−1.26 to 0.19	No	0.2	−0.17 to 0.58	No
Verbal IQ	IQ	−0.72	−1.97 to 0.54	No	−0.29	−0.91 to 0.32	No
Memory IQ	IQ	0.14	−0.97 to 1.25	No	−0.08	−0.7 to 0.54	No
Secondary outcomes							
Motor development (M-ABC-2)	PR	−0.62	−3.63 to 2.38	No	−0.4	−1.99 to 1.18	No
Attention							
CPT reaction time	z	0.07	−0.06 to 0.2	No	−0.05	−0.12 to 0.01	No
CPT omission errors	z	0.03	−0.04 to 0.1	No	0	−0.04 to 0.03	No
CPT commission errors	z	0.07	−0.06 to 0.2	No	−0.05	−0.12 to 0.01	No
Emotional excitability (PFK)	z	0.01	−0.1 to 0.11	No	0.02	−0.03 to 0.07	No
ADHD symptoms							
ADHD global score	z	−0.01	−0.1 to 0.08	No	−0.03	−0.06 to 0.01	No
ADHD hyperactivity	z	−0.02	−0.12 to 0.07	No	0.01	−0.04 to 0.05	No
ADHD inattention	z	0	−0.1 to 0.1	No	−0.04	−0.07 to 0	No
Behavioral difficulties							
CBCL global score	z	−0.05	−0.16 to 0.06	No	−0.03	−0.09 to 0.03	No
CBCL internalizing	z	0.06	−0.04 to 0.17	No	0.03	−0.02 to 0.09	No
CBCL externalizing	z	0.08	−0.03 to 0.18	No	−0.01	−0.06 to 0.04	No
Strength and difficulties (SDQ)	Raw	−0.55	−1.1 to 0	No	−0.23	−0.5 to 0.03	No
Electrocortical activity							
Frontal	SEF	0.02	−0.19 to 0.23	No	0.02	−0.08 to 0.11	No
Temporal	SEF	−0.12	−0.27 to 0.02	No	−0.03	−0.09 to 0.04	No
Parietal	SEF	−0.06	−0.3 to 0.18	No	0.01	−0.09 to 0.12	No
Occipital	SEF	−0.21	−0.47 to 0.05	No	−0.08	−0.21 to 0.04	No

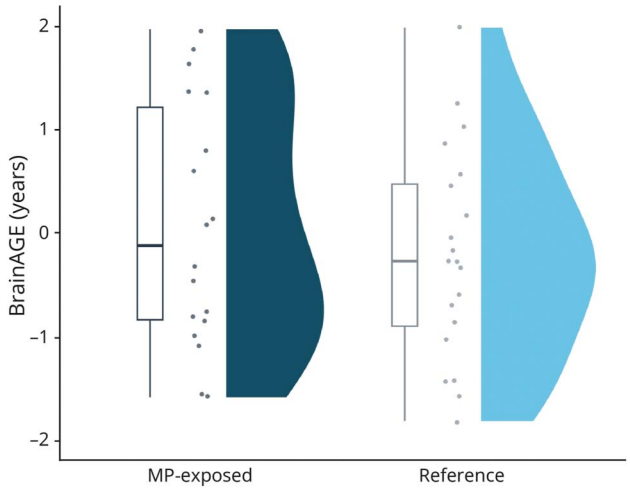
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CBCL = child behavior checklist; CPT = Continuous Performance Test; M-ABC-2 = Movement Assessment Battery for Children, Second Edition; MP = methylprednisolone; PFK = German personality questionnaire; PR = percentile rank; SDQ = Strengths and Difficulties Questionnaire; SEF = spectral edge frequency.
"Evidence of association" indicates whether the 95% CI for the regression coefficient includes zero; intervals excluding zero are interpreted as evidence of an association.
Robust linear regression analysis. Neuropsychological outcomes: Lower values denote worse performance/outcomes, results adjusted for socioeconomic background and child sex. Electrocortical activity: Results adjusted for child age and sex.

Discussion

This study assessed the long-term neurodevelopmental consequences of intrauterine exposure to maternal MS relapse treatment with the glucocorticoid MP using comprehensive neurocognitive testing, electrocortical measures of functional brain maturation, and well-established neuroimaging-derived biomarkers of structural brain development. Besides its methodologic rigor, a key strength of our study lies in the well-defined cohort, which included children born at term and balanced in terms of sociodemographic background, which minimizes the confounding factors associated with the neurodevelopmental outcomes. Contrary to our hypothesis, we did not observe a significant association between maternal MS relapse therapy with MP and neurodevelopmental outcomes in school-aged children.

Physiologic levels of glucocorticoids play a critical role in normal brain development, by regulating neural stem cell differentiation and influencing neurogenesis, synaptogenesis, and myelination.[7] However, excessive glucocorticoid exposure during vulnerable periods of fetal development can modify these processes. It has been hypothesized that elevated maternal stress hormone levels during pregnancy may indicate an anticipated stressful postnatal environment, triggering neurodevelopmental adaptations. However, this adaptation comes at a cost because it is associated with an increased risk of neurodevelopmental disorders later in life,[7,30] a phenomenon known as "fetal programming of health and disease."[31]

Figure 4 Distribution of BrainAGE Scores



The MRI-derived BrainAGE score reflects deviations from the chronological brain age in a normative population. The figure presents standard boxplots with whiskers extending to 1.5 times the interquartile range. Dots represent individual BrainAGE scores, and density curves illustrate their distribution.

Animal studies in rodents, sheep, and nonhuman primates have consistently demonstrated that prenatal exposure to synthetic glucocorticoids (e.g., dexamethasone or betamethasone) or supraphysiological endogenous glucocorticoid exposure elicited during maternal psychosocial stress can significantly alter the developmental trajectory of the fetal brain.[7,32] Effects include changes in cytoskeletal proteins,[33] delayed myelination,[34] impaired hippocampal plasticity,[35] reduced brain weight, and dendritic growth, leading to cognitive deficits, anxiety, and dysregulated stress responses.[32,36]

Human studies suggest similar neurodevelopmental risks as animal studies.[37,38] For example, prenatal betamethasone treatment for respiratory distress syndrome prevention has been linked to reduced head circumference in newborns[39] and, based on volumetric MRI, to a decrease in brain surface area and cortical surface complexity in both infants[40] and school-aged children,[11] suggesting an increased vulnerability to cognitive and behavioral impairments. In fact, prenatal exposure to betamethasone has been linked to lower IQ scores in 8- to 9-year-old children in a dose-dependent manner.[8] In another study, prenatal exposure to synthetic glucocorticoids for fetal lung maturation was associated with higher risks of ADHD and emotional difficulties in 8-year-old children.[41] Notably, the elevated risk of psychiatric disorders has been reported to persist into the fourth decade of life.[42] However, not all studies have demonstrated an increased neurodevelopmental risk after antenatal glucocorticoid exposure. For example, 2 large follow-up studies reported no significant differences in cognitive outcomes at school age[43] and at age 31 years,[44] following a single course of antenatal betamethasone.

The lack of significant associations between MS relapse treatment with MP and functional and structural neurodevelopmental outcomes in our study, compared with previous findings, may be attributed to the specific characteristics of MP placental transfer or the timing of MP exposure. Although the overall median dose of MP in our study was considerably higher than that regularly used for fetal lung maturation (5 g MP intravenously over 5 days vs 24 mg betamethasone intramuscularly within 24 hours[37]), MP's pharmacologic potency is estimated to be 4–5 times lower than that of betamethasone.[41] Furthermore, unlike betamethasone, which is fluorinated, highly

lipophilic, and resistant to placental inactivation, MP undergoes significant metabolism during transplacental passage using the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2),[45] which likely further limits its fetal impact. However, the exact extent of placental MP transfer remains unclear. Although in vitro data indicate that approximately 90% of MP is inactivated by 11β-HSD-2,[45] in vivo data suggest that more than 40% of intravenously administered MP reaches the fetal circulation in its active form when given shortly before delivery.[46]

To examine whether an increased MP dosage can overcome the placental barrier, we analyzed a potential dose-response relationship between MP exposure and functional brain development, as previously observed for betamethasone in obstetric settings.[8] In contrast to these findings, our analysis did not reveal any association between total MP dose and functional brain development, including IQ, secondary neuropsychological outcomes, and electrocortical activity. However, the number of children with very high MP exposure (>5 g) in our cohort was too small to draw statistically robust conclusions. As both animal and human data suggest a dose-response relationship between prenatal glucocorticoid exposure and neurocognitive performance, it would be desirable to examine this association in a larger cohort. Of note, because of even lower statistical power, this analysis could not be extended to MRI-based outcomes.

The importance of the timing of MP exposure is reflected in the changing permeability of the placental barrier to glucocorticoids during pregnancy, which increases toward the end of pregnancy.[47] In addition, brain development follows highly orchestrated regional and temporal patterns, with specific periods of vulnerability that vary depending on the timing of glucocorticoid exposure.[48] Although the precise windows of susceptibility remain to be fully established,[48] most studies on the long-term neurodevelopmental effects of fetal glucocorticoid exposure focus on the third trimester, when betamethasone is administered to enhance fetal lung maturation[8,11,49] and the placental permeability to glucocorticoids is higher.[47] By contrast, the majority of MP exposures in our study occurred during the second trimester of pregnancy. However, our exploratory post hoc analysis did not reveal an association between the timing of MP exposure and neurodevelopmental outcomes.

Although the sample size was sufficient for the primary end point, it was limited for secondary end points, restricting the ability to detect subtle associations and increasing the risk of type II errors. Consequently, we were unable to robustly investigate either linear or nonlinear relationships between the timing of exposure and brain development. The sample size was also insufficient to assess potential sex-specific associations with prenatal glucocorticoid exposure, as suggested by previous findings from animal studies and human cohorts.[50] To adequately address these open questions, a larger study will be required. Given the challenges we encountered in identifying and recruiting sufficient numbers of prenatally exposed children many years after maternal MP treatment despite having access to one of the largest national MS pregnancy registries worldwide, such an effort would necessitate coordinated international collaboration. The reliance on parental reporting for some neuropsychological measures may introduce subjective bias; however, the use of validated instruments and complementary objective tests helps mitigate this concern. The sample consisted exclusively of participants of White/European descent, limiting the generalizability of findings to more ethnically diverse populations. Finally, the retrospective study design inherently limits the ability to control for all potential confounders, which leaves open the possibility of residual confounding.

This study addresses a previously underexplored question concerning the associations of high-dose MP treatment during pregnancy with offspring brain development. Although no statistically significant associations were found between prenatal MP exposure and functional or structural neurodevelopmental outcomes in school-aged children, this study's limitations do not allow for firm conclusions regarding subtle or developmentally emergent effects. Given the well-documented influence of glucocorticoids on neurodevelopment, particularly in later gestation, we propose that MP should be used with caution and at the lowest effective dose. Furthermore, with increasing evidence supporting the safety of certain DMTs during pregnancy, their use should be prioritized over MP whenever possible, until larger prospective studies confirm our findings. Importantly, these studies should extend beyond puberty, as adverse effects on brain development may only become apparent in adolescence or adulthood.

Acknowledgement

The authors gratefully acknowledge the assistance of Dr. Daniel Güllmar in the design and optimization of the MRI protocol.

Author Contributions

V. Kozik: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Dreiling: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D. Müller: major role in the acquisition and analysis of data. O. Tiedge: major role in the acquisition of data. R. Schneider: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Thiel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Bellenberg: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Krieger: drafting/revision of the manuscript for content, including medical writing for content; major role in the

acquisition of data. C. Lukas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H.-J. Mentzel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Gaser: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Hellwig: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Schwab: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. F. Rakers: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This study is supported by the Grant for Multiple Sclerosis Innovation 2020 (Merck Healthcare KGaA).

Disclosure

V. Kozik is funded by the German Federal Ministry of Research, Technology and Space (BMFTR; Center for Early Pregnancy and Reproductive Health, CEPRE; funding reference: 01GR2305A). M. Dreiling received sponsorship for congress participation from Jazz Pharmaceuticals and is funded by the German Research Foundation (DFG; Clinician Scientist Program OrganAge; funding reference 413668513). D. Müller and O. Tiedge report no disclosures relevant to the manuscript. R. Schneider has received consulting and speakers' honoraria from Roche Pharma AG, Novartis Pharma, Merck KGaA, and Alexion Pharma; and has received research scientific grant support from Novartis Pharma. S. Thiel received speakers' honoraria from Bayer Healthcare and Biogen GmbH; payment for manuscript writing from HEXAL AG; and sponsorship for congress participation from Biogen GmbH. B. Bellenberg and B. Krieger report no disclosures relevant to the manuscript. C. Lukas received consulting and speaker honoraria from Biogen Idec, Bayer Schering, BMS, Daiichi Sankyo, Merck Serono, Novartis, Sanofi, Genzyme, and TEVA; and has received a research grant from the German Federal Ministry for Education and Research (BMBF), German Competence Network Multiple Sclerosis (KKNMS), grant no. 01GI1601I. H.-J. Mentzel and C. Gaser report no disclosures relevant to the manuscript. K. Hellwig received speakers' honoraria and served on advisory boards for TEVA, BMS, Roche, Merck, and Mylan; and received research sponsorships form Roche, Biogen, Genzyme, Novartis, and BMS. M. Schwab received funding for travel or speaker honoraria and has served on advisory boards for Janssen, Almirall, Bayer Healthcare, Biogen, BMS, Sanofi-Genzyme, Merck Healthcare, Novartis, Roche, HEXAL AG, and TEVA; and received research support from Novartis and Bayer Healthcare. F. Rakers has received research grants from Merck KGaA and Biogen GmbH; speaker honoraria from Merck KGaA, Biogen GmbH, BMS GmbH, Roche GmbH, and Novartis GmbH; and travel funding from Merck KGaA and Biogen GmbH. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® April 11, 2025. Accepted in final form August 4, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Courtney Wusthoff, MD, MS.

References

1. Dobson R, Dassan P, Roberts M, Giovannoni G, Nelson-Piercy C, Brex PA. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. *Pract Neurol*. 2019;19(2):106-114. doi:10.1136/practneurol-2018-002060
2. Dobson R, Rog D, Ovadia C, et al. Anti-CD20 therapies in pregnancy and breast feeding: a review and ABN guidelines. *Pract Neurol*. 2023;23(1):6-14. doi:10.1136/pn-2022-003426
3. Bast N, Dost-Kovalsky K, Haben S, et al. Impact of disease-modifying therapies on pregnancy outcomes in multiple sclerosis: a prospective cohort study from the German multiple sclerosis and pregnancy registry. *Lancet Reg Health Eur*. 2025;48:101137. doi:10.1016/j.lanepe.2024.101137
4. Houtchens MK, Manieri MC, Mahlanza TD, et al. A real-world prospective multiple sclerosis pregnancy registry in the United States: PREG-MS. *Neurol Clin Pract*. 2025;15(2):e200425. doi:10.1212/CPJ.0000000000200425
5. Houtchens MK, Edwards NC, Phillips AL. Relapses and disease-modifying drug treatment in pregnancy and live birth in US women with MS. *Neurology*. 2018;91(17):e1570-e1578. doi:10.1212/WNL.0000000000006382
6. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler J*. 2018;24(2):96-120. doi:10.1177/1352458517751049
7. Moisiadis VG, Matthews SG. Glucocorticoids and fetal programming part 2: mechanisms. *Nat Rev Endocrinol*. 2014;10(7):403-411. doi:10.1038/nrendo.2014.74
8. Rakers F, Schleußner E, Muth I, et al. Association between antenatal glucocorticoid exposure and the activity of the stress system, cognition, and behavior in 8- to 9-year-old children: a prospective observational study. *Acta Obstet Gynecol Scand*. 2022;101(9):996-1006. doi:10.1111/aogs.14386
9. ter Wolbeek M, de Sonneville LMJ, de Vries WB, et al. Early life intervention with glucocorticoids has negative effects on motor development and neuropsychological function in 14-17 year-old adolescents. *Psychoneuroendocrinology*. 2013;38(7):975-986. doi:10.1016/j.psyneuen.2012.10.001
10. Rakers F, Schleussner E, Cornelius A, et al. Association between prenatal glucocorticoid exposure and adolescent neurodevelopment: an observational follow-up study. *Acta Obstet Gynecol Scand*. 2024;103(8):1530-1540. doi:10.1111/aogs.14885
11. Davis EP, Sandman CA, Buss C, Wing DA, Head K. Fetal glucocorticoid exposure is associated with preadolescent brain development. *Biol Psychiatry*. 2013;74(9):647-655. doi:10.1016/j.biopsych.2013.03.009
12. Kozik V, Schwab M, Thiel S, Hellwig K, Rakers F, Dreiling M. Protocol for a cross-sectional study: effects of a multiple sclerosis relapse therapy with methylprednisolone on offspring neurocognitive development and behavior (MS-children). *Front Neurol*. 2022;13:830057. doi:10.3389/fneur.2022.830057
13. Franke K, Luders E, May A, Wilke M, Gaser C. Brain maturation: predicting individual BrainAGE in children and adolescents using structural MRI. *Neuroimage*. 2012;63(3):1305-1312. doi:10.1016/j.neuroimage.2012.08.001
14. Thiel S, Ciplea AI, Gold R, Hellwig K. The German Multiple Sclerosis and Pregnancy Registry: rationale, objective, design, and first results. *Ther Adv Neurol Disord*. 2021;14:17562864211054956. doi:10.1177/17562864211054956
15. Steinhausen H-C, Metzke CW. Die Zürcher Lebensereignis-Liste (ZLEL): Ergebnisse einer Schweizer epidemiologischen Untersuchung. *Kind Entwickl*. 2001;10(1):47-55. doi:10.1026//0942-5403.10.1.47
16. Hagmann-von Arx P, Grob A. *RIAS-Reynolds Intellectual Assessment Scales and Screening: deutschsprachige Adaptation der Reynolds Intellectual Assessment Scales (RIAS) & des Reynolds Intellectual Screening Test (RIST) von Cecil R. Reynolds und Randy W. Kamphaus: Manual*. Hans Huber; 2014.
17. Halperin JM, Sharma V, Greenblatt E, Schwartz ST. Assessment of the Continuous Performance Test: reliability and validity in a nonreferred sample. *Psychol Assess*. 1991;3(4):603-608. doi:10.1037/1040-3590.3.4.603
18. Seitz W, Rausche A. *Persönlichkeitsfragebogen für Kinder zwischen 9 und 14 Jahren: PFK 9-14*. Hogrefe: Verlag für Psychologie; 1992.
19. Döpfner M, Görtz-Dorten A, Lehmkuhl G. *Diagnostik-System für Psychische Störungen Nach ICD-10 und DSDM-5 für Kinder und Jugendliche-III (DISYPS-III)*. Hogrefe; 2017.
20. Döpfner M, Checklist ADCB. *Elternfragebogen über das Verhalten von Kindern und Jugendlichen: deutsche Bearbeitung der Child Behavior Checklist (CBCL/4-18)*. Einführung und Anleitung zur Handauswertung: Arbeitsgruppe Kinder-, Jugend-und Familiendiagnostik, 1998.
21. Lohbeck A, Schultheiß J, Petermann F, Petermann U. Die deutsche Selbstbeurteilungsversion des Strengths and Difficulties Questionnaire (SDQ-Deu-S). *Diagnostica*. 2015;61:222-235.
22. Brown T, Lalor A. The Movement Assessment Battery for Children—second edition (MABC-2): a review and critique. *Phys Occup Ther Pediatr*. 2009;29(1):86-103. doi:10.1080/01942630802574908

23. Szeto HH, Vo TD, Dwyer G, Dogramajian ME, Cox MJ, Senger G. The ontogeny of fetal lamb electrocortical activity: a power spectral analysis. *Am J Obstet Gynecol*. 1985; 153(4):462-466. doi:10.1016/0002-9378(85)90088-2
24. Cragg L, Kovacevic N, McIntosh AR, et al. Maturation of EEG power spectra in early adolescence: a longitudinal study. *Dev Sci*. 2011;14(5):935-943. doi:10.1111/j.1467-7687.2010.01031.x
25. Gaser C. *Manual Computational Anatomy Toolbox CAT12 [online]*. Accessed January 2, 2025. neuro-jena.github.io/cat12-help/.
26. Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. *Neuroimage*. 2013;65:336-348. doi:10.1016/j.neuroimage.2012.09.050
27. Luders E, Thompson PM, Narr KL, Toga AW, Jancke L, Gaser C. A curvature-based approach to estimate local gyrification on the cortical surface. *Neuroimage*. 2006; 29(4):1224-1230. doi:10.1016/j.neuroimage.2005.08.049
28. Franke K, Gaser C. Ten years of BrainAGE as a neuroimaging biomarker of brain aging: what insights have we gained? *Front Neurol*. 2019;10:789. doi:10.3389/fneur.2019.00789
29. Kalc P, Dahnke R, Hoffstaedter F, Gaser C; Alzheimer's Disease Neuroimaging Initiative. BrainAGE: revisited and reframed machine learning workflow. *Hum Brain Mapp*. 2024;45(3):e26632. doi:10.1002/hbm.26632
30. Rakers F, Rupprecht S, Dreiling M, Bergmeier C, Witte OW, Schwab M. Transfer of maternal psychosocial stress to the fetus. *Neurosci Biobehav Rev*. 2020;117:185-197. doi:10.1016/j.neubiorev.2017.02.019
31. Suzuki K. The developing world of DOHaD. *J Dev Orig Health Dis*. 2018;9(3): 266-269. doi:10.1017/S2040174417000691
32. Fitzgerald E, Parent C, Kee MZ, Meaney MJ. Maternal distress and offspring neurodevelopment: challenges and opportunities for pre-clinical research models. *Front Hum Neurosci*. 2021;15:635304. doi:10.3389/fnhum.2021.635304
33. Antonow-Schlorke I, Schwab M, Li C, Nathanielsz PW. Glucocorticoid exposure at the dose used clinically alters cytoskeletal proteins and presynaptic terminals in the fetal baboon brain. *J Physiol*. 2003;547(pt 1):117-123. doi:10.1113/jphysiol.2002.025700
34. Antonow-Schlorke I, Helgert A, Gey C, et al. Adverse effects of antenatal glucocorticoids on cerebral myelination in sheep. *Obstet Gynecol*. 2009;113(1):142-151. doi:10.1097/AOG.0b013e3181924d3b
35. Setiawan E, Jackson MF, MacDonald JF, Matthews SG. Effects of repeated prenatal glucocorticoid exposure on long-term potentiation in the juvenile guinea-pig hippocampus. *J Physiol*. 2007;581(pt 3):1033-1042. doi:10.1113/jphysiol.2006.127381
36. Peffer ME, Zhang JY, Umfrey L, Rudine AC, Monaghan AP, DeFranco DB. Minireview: the impact of antenatal therapeutic synthetic glucocorticoids on the developing fetal brain. *Mol Endocrinol*. 2015;29(5):658-666. doi:10.1210/me.2015-1042
37. Sarid EB, Stoopler ML, Morency A-M, Garfinkle J. Neurological implications of antenatal corticosteroids on late preterm and term infants: a scoping review. *Pediatr Res*. 2022;92(5):1225-1239. doi:10.1038/s41390-022-02135-3
38. Van den Bergh BRH, van den Heuvel MI, Lahti M, et al. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. *Neurosci Biobehav Rev*. 2020;117:26-64. doi:10.1016/j.neubiorev.2017.07.003
39. Rodriguez A, Wang Y, Ali Khan A, Cartwright R, Gissler M, Järvelin M-R. Antenatal corticosteroid therapy (ACT) and size at birth: a population-based analysis using the Finnish Medical Birth Register. *PLoS Med*. 2019;16(2):e1002746. doi:10.1371/journal.pmed.1002746
40. Modi N, Lewis H, Al-Naqeeb N, Ajayi-Obe M, Doré CJ, Rutherford M. The effects of repeated antenatal glucocorticoid therapy on the developing brain. *Pediatr Res*. 2001; 50(5):581-585. doi:10.1203/00006450-200111000-00008
41. Khalife N, Glover V, Taanila A, Ebeling H, Järvelin MR, Rodriguez A. Prenatal glucocorticoid treatment and later mental health in children and adolescents. *PLoS One*. 2013;8(11):e81394. doi:10.1371/journal.pone.0081394
42. Savoy C, Ferro MA, Schmidt LA, Saigal S, Van Lieshout RJ. Prenatal betamethasone exposure and psychopathology risk in extremely low birth weight survivors in the third and fourth decades of life. *Psychoneuroendocrinology*. 2016;74:278-285. doi:10.1016/j.psyneuen.2016.09.021
43. Gyamfi-Bannerman C, Clifton RG, Tita ATN, et al. Neurodevelopmental outcomes after late preterm antenatal corticosteroids: the ALPS follow-up study. *JAMA*. 2024; 331(19):1629-1637. doi:10.1001/jama.2024.4303
44. Dalziel SR, Lim VK, Lambert A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. *BMJ*. 2005;331(7518):665. doi:10.1136/bmj.38576.494363.E0
45. van Runnard Heimel PJ, Franx A, Schobben AFAM, Huisjes AJM, Derks JB, Bruinse HW. Corticosteroids, pregnancy, and HELLP syndrome: a review. *Obstet Gynecol Surv*. 2005;60(1):57-74. doi:10.1097/01.ogx.0000150346.42901.07
46. Anderson GG, Rotchell Y, Kaiser DG. Placental transfer of methylprednisolone following maternal intravenous administration. *Am J Obstet Gynecol*. 1981;140(6): 699-701. doi:10.1016/0002-9378(81)90207-6
47. Zhu P, Wang W, Zuo R, Sun K. Mechanisms for establishment of the placental glucocorticoid barrier, a guard for life. *Cell Mol Life Sci*. 2019;76(1):13-26. doi: 10.1007/s00018-018-2918-5
48. Collins JM, Keane JM, Deady C, et al. Prenatal stress impacts foetal neurodevelopment: temporal windows of gestational vulnerability. *Neurosci Biobehav Rev*. 2024;164:105793. doi:10.1016/j.neubiorev.2024.105793
49. MacArthur B, Howie R, Dezoete J, Elkins J. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics*. 1982;70(1):99-105. doi:10.1542/peds.70.1.99
50. Glover V, Hill J. Sex differences in the programming effects of prenatal stress on psychopathology and stress responses: an evolutionary perspective. *Physiol Behav*. 2012;106(5):736-740. doi:10.1016/j.physbeh.2012.02.011