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Prenatal triptan exposure and neurodevelopmental outcomes in 5-year-old children: Follow-up from the Norwegian Mother and Child Cohort Study

Gerd-Marie Eskerud Harris[1] | Mollie Wood[1] | Eivind Ystrom[1,2,3] | Hedvig Nordeng[1,4]

[1]Pharmacoepidemiology & Drug Safety Research Group, School of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway

[2]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway

[3]Department of Psychology, University of Oslo, Oslo, Norway

[4]Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

Correspondence
Gerd-Marie Eskerud Harris, Pharmacoepidemiology & Drug Safety Research Group, School of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway.
Email: g.m.e.harris@farmasi.uio.no

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Abstract

Background: Triptans are commonly used to treat migraine headaches, but data on the long-term safety of these medications during pregnancy are sparse. Triptans have a biologically plausible mechanism for effects on the fetal brain through binding to 5-HT_1-receptors, and previous studies show increased risks of externalising behaviour problems in toddlers exposed to triptans during pregnancy.

Methods: We included 3784 children in the Norwegian Mother and Child Cohort Study, whose mothers returned the 5-year-questionnaire and reported a history of migraine or triptan use; 353 (9.3%) mothers reported use of triptans during pregnancy, 1509 (39.9%) reported migraine during pregnancy but no triptan use, and 1922 (50.8%) had migraine prior to pregnancy only. We used linear and log-binomial models with inverse probability weights to examine the association between prenatal triptan exposure and internalising and externalising behaviour, communication, and temperament in 5-year-old children.

Results: Triptan-exposed children scored higher on the sociability trait than unexposed children of mothers with migraine (β 1.66, 95% confidence interval [0.30, 3.02]). We found no other differences in temperament, or increased risk of behaviour or communication problems.

Conclusions: Contrary to results from previous studies in younger children, we found no increased risk of externalising behaviour problems in 5-year-old children exposed to triptans in fetal life. Triptan-exposed children did have slightly more sociable temperaments, but the clinical meaning of this finding is uncertain.

KEYWORDS
behaviour, child, MoBa, neurodevelopment, pregnancy, triptans

1 | INTRODUCTION

The reproductive safety of medications cannot be assured without considering long-term effects on the child. Fetal neurodevelopment begins in pregnancy and continues into the first years of life. Childhood symptoms of emotional and behaviour problems are predictive of mental health problems in adolescence.[1,2] Triptans, which are serotonin (5-$HT_{1B/D}$) agonists used to treat migraine, have a plausible mechanism for effects on the fetal brain, as these receptors play important roles in the regulation of fetal development of the central nervous system.[3]

Migraine affects approximately 20% of women of reproductive age,[4] and triptans are used by 15%-25% of pregnant women with migraine.[5,6] Most previous studies on triptan safety in pregnancy have focused on immediate pregnancy outcomes. A recent meta-analysis found no increased risk of malformations or prematurity for triptan

exposure in the first trimester and beyond, but a potential increased risk for spontaneous abortion.[7] The meta-analysis did note an increased risk for malformations for women with migraine who did not use triptans, suggesting that for immediate pregnancy outcomes, failing to treat migraine may pose a greater risk to the child.[7] Women with migraine also have higher risk of preeclampsia.[8] Although less effective than triptans, paracetamol is the recommended antimigraine treatment during pregnancy, but recent research suggests a possible link between long-term paracetamol intake in pregnancy and childhood symptoms of neurodevelopmental problems,[9,10] diagnosis of attention deficit hyperactivity disorder (ADHD),[11] and hyperkinetic disorder.[10]

We have previously investigated the association between prenatal triptan exposure and neurodevelopment in children aged 18 months and 3 years, using parent-reported data from the Norwegian Mother and Child Cohort Study (MoBa). We found an increased risk of externalising behaviour in triptan-exposed children at 3 years, compared with migraine controls (RR 1.36, 95% CI [1.02, 1.81]), but no increased risk of internalising behaviour.[12] The increased rates of externalising behaviour were apparent already at 18 months.[13] Other outcomes investigated were psychomotor, communication, and temperament problems at 3 years of age, none of which were associated with prenatal triptan exposure after adjusting for migraine severity.[14] The association between triptan exposure in pregnancy and child neurodevelopment has not been examined in other studies.

Following these studies, our aim was to investigate the association between triptan exposure in pregnancy and externalising behaviour, internalising behaviour, communication, and temperament in 5-year-old children in the MoBa, using psychometric instruments that are internationally recognised in the field of psychology to assess these traits.

2 | METHODS

2.1 | Population and data collection

This study used data from the Norwegian Mother and Child Cohort Study (MoBa), linked to the Medical Birth Registry of Norway (MBRN) (Data Version 9, released November 2015). MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health that includes data on over 100 000 mother-child pairs.[15] All women in Norway who were pregnant between 1999 and 2008 received a postal invitation to participate prior to their routine ultrasound examination in gestational week 17-18. The initial participation rate was 41%. Mothers younger than 25 years, those living alone, mothers with more than 2 previous births, mothers with previous stillbirth, and smokers were under-represented; and mothers taking folate supplements and multivitamins were over-represented.[16] Follow-up is conducted via questionnaires in pregnancy weeks 17, 22, and 30, and at child's age 6 and 18 months, 3 and 5 years, and onward. Using each participant's personal identification number, the MoBa data are linked to the MBRN, which includes information on pregnancy, delivery, and the health of the neonate for all births in Norway.[17]

For the current study, we required women to have completed the questionnaires with information on medication exposure in pregnancy (Q1, Q3, and Q4), as well as the questionnaire at child age 5 years (Q5y). A total of 90.7% of the women who originally consented completed Q1. Of those, 91.3% also completed Q3, and 90.0% completed Q4. Q5y was returned by 45.7% of these women. As this study focused on neurodevelopment, we excluded infants not born alive. Women with undefined exposure (ie, reported migraine and indicated that a drug was taken, but not which drug) or with unknown triptan timing (reported triptan use, but not whether it was used before or during pregnancy) were also excluded, as well as twins and triplets. Women with unknown triptan timing during pregnancy were included. An overview of drop-out and exclusion criteria is presented in Figure 1. The analytic sample consisted of 37 656 children whose mothers completed Q5y, of which 2697 (7.2%) had missing covariates and were excluded. In the remaining complete case sample of 34 959 children, 3784 (10.8%) of the mothers reported to have migraine.

2.2 | Triptan exposure

Medication use in pregnancy was reported in Q1 (6 months prepregnancy and gestational weeks 0-13+), Q3 (week 13-29+), and Q4 (week 30-end of pregnancy) for specific indications. Drug exposure was coded in groups based on the Anatomical Therapeutic Chemical (ATC) Classification System.[18] The exposed group included children of women who reported use of triptans in pregnancy, defined as reporting of ATC code N02CC under any of the indications that were mentioned in the questionnaires, as triptans are used exclusively for migraine. In the first questionnaire, women could report if they had migraine before and/or during pregnancy. Based on this information, we defined 2 non-exposed comparison groups; (i) children whose mothers reported migraine in pregnancy that were not treated with triptans, and (ii) children of mothers who reported migraine before pregnancy only, as shown in Figure 1. When studying long-term outcomes such as neurodevelopment, triptan exposure during the entire pregnancy is aetiologically relevant.

2.3 | Neurodevelopmental outcomes

The Child Behaviour Checklist (CBCL) is a widely used method of identifying behavioural and emotional problems in children. A short version was used in the MoBa.[19] We included the externalising domain (consisting of the subscales 'attention problems' and 'aggressive behaviour') and the internalising domain (consisting of the subscales 'emotionally reactive', 'anxious/depressed', and 'somatic complaints'). Clinically significant externalising behaviour problems and internalising behaviour problems were defined as T-scores of 63 or greater, as recommended.[20]

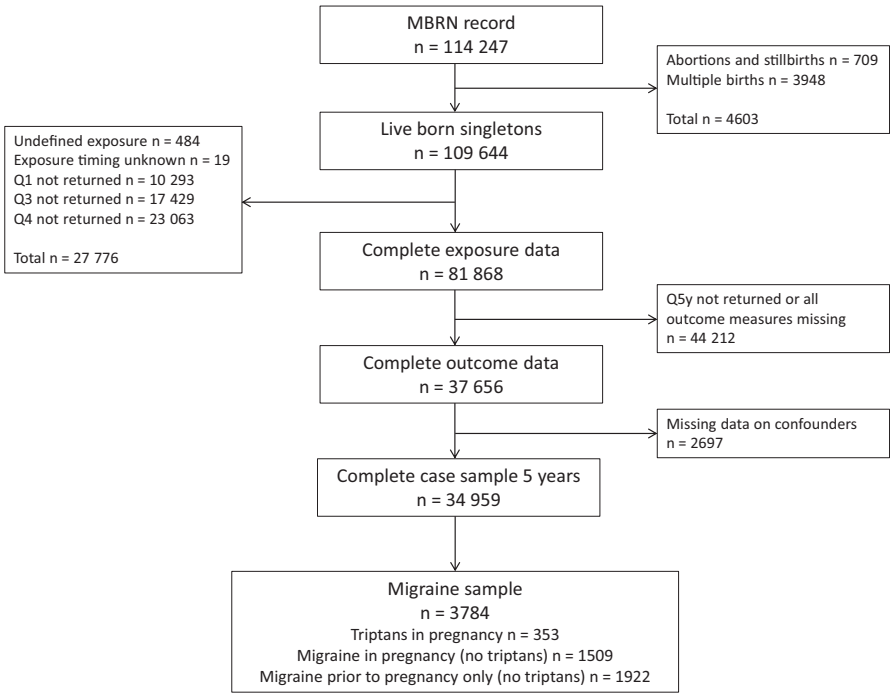

FIGURE 1 Overview of the study sample

The Ages and Stages Questionnaire (ASQ) is a screening tool used to detect developmental delays in 5 domains; however, the five-year questionnaire in the MoBa only includes the communication domain, which has 7 questions regarding the child's language competence.[21] Communication problems were defined as children with T-scores of 65 or greater.[22]

The Emotionality Activity and Shyness Temperament Questionnaire (EAS) measures 4 temperament traits: emotionality (the tendency to become emotionally aroused easily and intensely), activity (preferred activity level), sociability (the tendency to prefer the presence of others to being alone), and shyness (the tendency to be awkward and inhibited in new social situations).[23] The short version used in the MoBa includes 12 statements, 3 in each domain.[24] As these are temperament traits, akin to normal personality in adults, there is no recommended cut-off. Higher T-scores indicate children who are more emotional, more active etc., relative to other children in the sample.

Additional information about scoring and items comprising the scales can be found in the supplementary material.

2.4 | Covariates

Potential confounders and risk factors for the outcomes were identified through literature review and directed acyclic graphs (DAGs)[25] (Figure S1). All covariates were categorised as presented in Table 1. Information on maternal age at delivery, marital status, parity, pregnancy complications (gestational diabetes and hypertensive disorders), child sex, birthweight, gestational age, and malformations was obtained from the MBRN. Highest level of completed and ongoing education, body mass index (BMI) before conception, folate intake before and during pregnancy (4 weeks prior to pregnancy and/or until week 12 in pregnancy), concomitant medication use, smoking habits, alcohol intake, and symptoms of depression or anxiety were self-reported in the MoBa questionnaires. An overview of the sources of the covariates can be found in Figure S2.

Symptoms of depression/anxiety were measured by a short version of the Hopkins Symptoms Checklist (SCL-5)[26] twice during pregnancy, and mean scores at each time point were standardised. Alcohol intake in pregnancy was classified as "No or minimal" (less than once per month), "Moderate" (once per month to once per week), and "Frequent" (more than once per week). Relevant co-medications were the following: analgesics in the ATC groups M01A (NSAIDs), N02BE01 (paracetamol), N02A (opioids); psychotropic drugs in ATC groups N05A (antipsychotics), N05BA (benzodiazepines), N05CF (benzodiazepine-like), N06A (antidepressants), N06BA (stimulants); and preventive migraine therapy in groups N06AA (tricyclic antidepressants), N03A (antiepileptic's), C07A (beta blockers), C09A (ACE-inhibitors), C09C (AII-blockers), and M03AX (botulinum toxin).

2.5 | Statistical analysis

We first determined the characteristics of women and children in the migraine sample, according to exposure group. In order to account for differences in the characteristics of women using triptans in pregnancy and those who did not, we used propensity score-based methods with inverse probability of treatment weights (IPTW).[27] Using logistic regression, we calculated the probability of taking triptans in pregnancy compared with (i) having migraine not treated with triptans, and (ii) having migraine prior to pregnancy only, conditional

on age, parity, education, marital status, pre-pregnancy BMI, concomitant medication use, mean SCL5-score, smoking, alcohol, folate intake, and child sex. We used the propensity scores to calculate stabilised IPTW, and checked that the covariates were sufficiently balanced between the exposed/unexposed groups; standardised differences less than 0.1 were considered acceptable.[27] In addition, stabilised inverse probability of censoring weights (IPCW) was estimated for each outcome in order to account for drop-out at 5 years, up-weighting the women who remain to represent similar women who drop-out.[28] These weights included the same variables as in the IPTW models, except smoking and alcohol, as models including these covariates resulted in extreme weights. We fit outcome models with the combined weights (IPTW multiplied by IPCW), using negative log-binomial regression for categorical outcomes (CBCL and ASQ), and linear regression for continuous outcomes (EAS). Robust variance estimation was applied to account for the weights.[27] The outcome models included children with complete outcome information, except for ASQ, where we also included those with 1 missing item out of the 7 included in the communication scale. We conducted an a priori sample size analysis in order to estimate detectable effect sizes, as described more detailed in the supplementary material.

We performed several sensitivity analyses. First, we repeated our main analysis in children whose mothers did not use paracetamol during pregnancy, in order to address potential residual confounding by paracetamol exposure. Second, we used probabilistic bias analysis to quantify the potential impact of selection bias from loss to follow-up.[29] We estimated associations between loss to follow-up and externalising behaviour problems by using selection proportions that we considered reasonable based on data at 3 years. For the probabilistic analysis, we used a trapezoidal distribution of the selection odds ratios with 10 000 simulations. Third, we did an analysis comparing the 2 unexposed groups (children of women with migraine during pregnancy vs children of women with migraine prior to pregnancy only) to look for differences in neurodevelopment related to active untreated migraine. Fourth, we modelled externalising and internalising behaviours and communication as continuous outcomes in order to better be able to pick up small but potentially meaningful differences in these outcomes.

Stata MP Version 14.1 was used in all analyses.

3 | RESULTS

3.1 | Description of the study sample

Of the 3784 women with migraine, 353 (9.3%) reported use of triptans during pregnancy, 1509 (39.9%) reported migraine in pregnancy but no use of triptans, and 1922 (50.8%) had migraine before pregnancy only. The most commonly used triptan was sumatriptan (Table S1). Maternal and child characteristics in the 3 groups before and after weighting are presented in Table 1. Women in the exposed group were slightly older than women in the comparison groups, and they were more likely to be first-time mothers compared with women with migraine in pregnancy not treated with triptans, but less likely to be first-time mothers compared with women with migraine prior to pregnancy only. There was little difference in other sociodemographic factors. Women using triptans reported a low to moderate alcohol intake in pregnancy more often than women in the comparison groups. They also used co-medications in pregnancy more frequently (see also Table S2). There was little difference in child characteristics such as preterm birth and congenital malformations. After weighting, all covariates included in the propensity scores were adequately balanced (Table 1). A comparison of the complete case sample with the full cohort is given in Table S3, including the amount of missingness for each covariate. Responses to all items on the CBCL and EAS, and at least 6 out of 7 items on the ASQ communication scale, were available for over 96% of the children in the migraine sample. For ASQ, 10.5% were missing 1 item on the communication scale, and these children were included in the analysis.

3.2 | Neurodevelopmental outcomes

We found no increased risk of externalising behaviour problems associated with triptan exposure in fetal life. In fact, we observed a lower risk of externalising problems for triptan-exposed children compared with children of women with untreated migraine (RR 0.68, 95% CI [0.44, 1.05]) and children of women with migraine prior to pregnancy only (RR 0.69, 95% CI [0.45, 1.07]), but the confidence intervals included 1 (Table 2). Children prenatally exposed to triptans scored higher on sociability traits than children of mothers with migraine not treated with triptans (β 1.66, 95% CI [0.30, 3.02]), although the difference in mean scores was small (T-score 51.0 vs. 49.6). This association was not observed for the comparison with children of mothers with migraine prior to pregnancy only (Table 3). We found no differences for other neurodevelopmental outcomes. We had limited power to detect relative risks between 0.5-1 (Table S4).

3.3 | Sensitivity analyses

Sensitivity analyses excluding women who used paracetamol revealed similarities and differences to the main analysis (Table S7 and S8). Most estimates in the restricted sample fell within the 95% confidence interval of the estimates from the main analysis, with the exception of sociability. An additional analysis comparing the 2 comparison groups showed no differences in neurodevelopment between children of women with migraine in pregnancy and children of women with migraine before pregnancy only (results not shown). As a further analysis to quantify the sensitivity of our finding for externalising behaviour problems to selection bias, we conducted a probabilistic bias analysis with selection associations based on the results in Table S6. We observed a corrected OR of 0.60 with a 95% confidence interval ranging from 0.46 to 0.89, compared with the conventional OR 0.67, 95% CI [0.43, 1.04].

TABLE 1 Baseline characteristics before and after IPT weighting in exposed and unexposed groups

	Triptans in pregnancy vs Migraine in pregnancy, no triptans				Triptans in pregnancy vs Migraine prior to pregnancy, no triptans			
	Before weighting		After weighting[a]		Before weighting		After weighting[a]	
	Exp. n = 353	Unexp. n = 1509	Exp. n = 353	Unexp. n = 1509	Exp. n = 353	Unexp. n = 1922	Exp. n = 353	Unexp. n = 1922
Maternal/pregnancy characteristics:								
Age at time of delivery, mean	31.4	30.6[b]	30.8	30.8	31.4	30.4[b]	30.7	30.6
Primiparous, %	52.1	45.3[b]	46.3	46.6	52.1	54.3[b]	54.2	54.3
Married/cohabiting, %	94.6	96.0	95.0	95.7	94.6	96.7[b]	95.6	96.3
College/university education, %	76.2	74.0	75.4	74.4	76.2	73.2	74.9	73.9
Pre-pregnancy BMI (kg/m^2), mean	24.3	24.3	24.3	24.3	24.3	23.1	24.1	24.0
Folic acid supplement, %	87.0	87.2	86.6	87.1	87.0	86.2	86.5	86.3
Depression/anxiety symptoms[c], mean	0.08	0.07	0.08	0.07	0.08	0.04	0.05	0.04
Hypertensive disorder[d], %	8.0	6.0	-	-	8.0	6.9	-	-
Gestational diabetes[d], %	0.9	1.0	-	-	0.9	0.5	-	-
Co-medications during pregnancy, %								
NSAIDs	23.5	15.7[b]	17.4	17.3	23.5	9.4[b]	13.2	12.5
Paracetamol	79.6	75.5	76.4	76.2	79.6	60.3[b]	66.8	63.6
Opioids	13.0	7.8[b]	9.0	8.8	13.0	2.4[b]	4.4	4.2
Preventive antimigraine therapy	1.7	0.5[b]	0.8	0.8	1.7	0.1[b]	0.3	0.7
Psychotropic drugs	6.5	3.0[b]	3.8	3.7	6.5	3.4[b]	4.2	4.4
Smoking, %								
No	84.4	89.3	80.7	80.0	84.4	78.5	79.3	78.6
Yes	4.8	5.5	5.1	5.5	4.8	4.8	5.8	4.8
Stopped	13.3	14.9	14.2	14.5	13.3	16.7	14.9	16.6
Alcohol intake, %								
No or minimal	84.4	89.3[b]	89.4	88.5	84.4	89.2[b]	89.9	88.6
Low to moderate	14.4	9.9[b]	9.8	10.7	14.4	10.1[b]	10.3	10.7
Frequent	1.1	0.8	0.9	0.9	1.1	0.7	0.7	0.7
Child characteristics:								
Boy, %	50.1	47.0	46.2	47.4	50.1	53.1	51.6	53.0
Preterm (<37 weeks)[d], %	3.4	4.2	-	-	3.4	4.5	-	-
Low birthweight (<2500 g)[d], %	2.0	2.1	-	-	2.0	3.0	-	-
Congenital malformations [d], %	3.4	4.3	-	-	3.4	4.8	-	-

Exp, exposed; unexp, unexposed.

[a]IPT weights calculated as the inverse predicted probability of taking triptans vs migraine in pregnancy and migraine prior to pregnancy, respectively, conditional on the covariates indicated in the table.

[b]Standardised differences above 0.1

[c]Symptoms of depression/anxiety measured by the 5-item version of the Hopkins Symptoms Checklist (SCI-5), using standardised mean of scores in Q1 and/or Q3.

[d]Not included in IPT weighting based on DAG.

When modelling externalising and internalising behaviours and communication as continuous outcomes, we observed findings consistent with the results of the main analysis. In particular, this analysis supported the trend towards a lower risk of externalising problems observed in the main analysis, as children exposed to triptans demonstrated slightly lower mean scores on the externalising behaviour scale compared with children in both comparison groups (Table S10).

TABLE 2 Associations of exposure to triptans in pregnancy with behaviour and communication at 5 years of age

	Total number, n	Number with outcome, % of n	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Child Behaviour Checklist:				
Externalising problems				
Triptans in pregnancy	340	7.4	0.69 (0.46, 1.04)	0.68 (0.44, 1.05)
Migraine in pregnancy	1457	10.6	1.00 (Reference)	1.00 (Reference)
Triptans in pregnancy	340	7.4	0.64 (0.43, 0.95)	0.69 (0.45, 1.07)
Migraine prior to pregnancy	1858	11.6	1.00 (Reference)	1.00 (Reference)
Internalising problems				
Triptans in pregnancy	343	12.2	1.07 (0.78, 1.47)	0.97 (0.68, 1.37)
Migraine in pregnancy	1482	11.4	1.00 (Reference)	1.00 (Reference)
Triptans in pregnancy	343	12.2	1.05 (0.77, 1.43)	0.92 (0.64, 1.31)
Migraine prior to pregnancy	1884	11.7	1.00 (Reference)	1.00 (Reference)
Ages and Stages Questionnaire:				
Communication problems				
Triptans in pregnancy	347	7.8	0.86 (0.58, 1.28)	0.77 (0.50, 1.18)
Migraine in pregnancy	1479	9.1	1.00 (Reference)	1.00 (Reference)
Triptans in pregnancy	347	7.8	1.05 (0.71, 1.56)	0.95 (0.61, 1.50)
Migraine prior to pregnancy	1885	7.4	1.00 (Reference)	1.00 (Reference)

RR, relative risk; CI, confidence interval.
Comparison groups 'Migraine in pregnancy' and 'Migraine prior to pregnancy' included women without use of triptans during pregnancy. Adjusted estimates are weighted according to IPTW multiplied by IPCW.

4 | COMMENT

4.1 | Principal findings

In this study of 3784 pregnant women with migraine and their children at 5 years of age, we found no increased risk of behaviour problems (internalising and externalising) or communication problems following prenatal triptan exposure. Rather, the risk of externalising behaviour problems seemed to be lower in the triptan-exposed children. Triptan-exposed children also scored higher on the sociability trait compared with unexposed children whose mothers had migraine during pregnancy, but not compared with children whose mothers had migraine prior to pregnancy only. We found no differences for other temperament traits (activity, emotionality, and shyness).

4.2 | Interpretation

Sociability is part of a broader personality domain, extraversion, and persons with higher levels of extraversion have lower risk of depression and anxiety disorders.[30] Activation of the 5-HT_{1A} receptor, related to antidepressant and anxiolytic effects, is associated with increased sociability in rats,[31] but it is unclear to what extent this impact on sociability extends to the 5-HT_{1B} and 5-HT_{1D} receptors, wherein triptans act as agonists. We observed higher sociability scores for triptan-exposed children only when compared with children whose mothers had migraine in pregnancy that were not treated with triptans. This finding was not robust in the sensitivity analysis of the restricted sample of children not exposed to paracetamol, and can therefore possibly be explained to some extent by residual confounding of paracetamol exposure. Thus, taking triptans in pregnancy may positively impact sociability in children; however, the clinical meaning of this finding is uncertain. Previous studies in younger children did not find any increased/decreased risk of temperament problems associated with prenatal triptan exposure.[14]

Previous research based on MoBa data showed an increased risk of externalising behaviour problems in 3-year-old children,[12] whereas we did not observe increased risks in 5-year-olds, rather a trend towards lower risk, and there could be several reasons for the different findings. First, the observed differences at 3 years may have resolved by age five, suggesting the triptan exposure results in early, but not persistent, behaviour problems. Second, 3-year-old children with externalising problems were less likely to be present at 5 years (53%) compared with 3-year-olds without problems (57%), and such problems could be driving the observed loss to follow-up. We took several steps to overcome potential selection bias arising from differential loss to follow-up, but we cannot rule out the possibility that this may explain the different findings. However, according to our probabilistic bias analysis, selection bias would have to be very strong in order to fully explain the results. The discrepancy in results could also be explained to some extent by differences in exposure definition. We used non-exposed comparison groups that might be more similar to the exposed group, and our study may therefore be better at accounting for underlying migraine severity. Previous studies in younger children did not find any increased risk of internalising

TABLE 3 Associations of exposure to triptans in pregnancy with temperament at 5 years of age

	Total number, n	Mean T-score (SD)	Unadjusted β (95% CI)	Adjusted β (95% CI)
Emotionality, Activity, and Shyness Temperament Questionnaire:				
Emotionality				
Triptans in pregnancy	345	49.7 (9.9)	−0.81 (−1.98, 0.37)	−1.02 (−2.33, 0.29)
Migraine in pregnancy	1483	50.5 (10.0)	0.00 (Reference)	0.00 (Reference)
Triptans in pregnancy	345	49.7 (9.9)	−0.82 (−1.99, 0.34)	−0.93 (−2.22, 0.42)
Migraine prior to pregnancy	1884	50.5 (10.2)	0.00 (Reference)	0.00 (Reference)
Activity				
Triptans in pregnancy	351	49.3 (10.2)	−0.80 (−1.99, 0.38)	−0.06 (−1.35, 1.23)
Migraine in pregnancy	1493	50.1 (10.2)	0.00 (Reference)	0.00 (Reference)
Triptans in pregnancy	351	49.3 (10.2)	−0.68 (−1.82, 0.47)	0.16 (−1.17, 1.49)
Migraine prior to pregnancy	1900	50.0 (10.0)	0.00 (Reference)	0.00 (Reference)
Shyness				
Triptans in pregnancy	348	50.1 (10.0)	−0.39 (−1.57, 0.79)	−0.71 (−2.08, 0.65)
Migraine in pregnancy	1480	50.5 (10.1)	0.00 (Reference)	0.00 (Reference)
Triptans in pregnancy	348	50.1 (10.0)	0.22 (−0.92, 1.37)	0.02 (−1.27, 1.32)
Migraine prior to pregnancy	1888	49.9 (10.0)	0.00 (Reference)	0.00 (Reference)
Sociability				
Triptans in pregnancy	349	51.0 (10.4)	1.34 (0.12, 2.56)	1.66 (0.30, 3.02)
Migraine in pregnancy	1492	49.6 (10.5)	0.00 (Reference)	0.00 (Reference)
Triptans in pregnancy	349	51.0 (10.4)	0.90 (−0.23, 2.04)	0.99 (−0.39, 2.37)
Migraine prior to pregnancy	1902	50.1 (9.9)	0.00 (Reference)	0.00 (Reference)

SD, standard deviation; CI, confidence interval. Comparison groups 'Migraine in pregnancy' and 'Migraine prior to pregnancy' include women without use of triptans during pregnancy. Adjusted estimates are weighted according to IPTW multiplied by IPCW.

behaviour or communication problems associated with prenatal triptan exposure,[12,14] which is in line with our findings in 5-year-olds.

4.3 | Strengths of the study

This study has several important strengths. MoBa is one of the largest population-based cohorts worldwide, following almost 40 000 pregnant women and their children until the age of 5. The prospective design and long follow-up allowed us to investigate potential long-term effects of medications in pregnancy, which is an important public health perspective given the increasing prevalence and burden of neurodevelopmental and psychiatric disorders in children.[32,33] Extensive information on neurodevelopment made it possible to examine several relevant outcomes, using established, well-validated psychometric instruments.[19,21,24] Furthermore, detailed information on a variety of characteristics was available in MoBa, including maternal sociodemographic and life style factors, mental health, and drug use, which are potential confounders for the relationship between triptan use in pregnancy and later neurodevelopmental problems in the child.

4.4 | Limitations of the data

There are also several limitations to consider. First, selection bias arising from loss to follow-up is a concern in MoBa as well as in other population-based cohort studies. Even though we used IPCW to up-weight women who remain in the sample to represent similar women who drop-out, we cannot rule out that selection bias might have affected our results: there could be unknown or unmeasured predictors of drop-out, such as migraine severity or genetic vulnerability. This should be kept in mind, along with the fact that neurodevelopmental problems in themselves also could be driving drop-out, as discussed. However, as shown in our probabilistic analysis, this is not likely to fully explain the findings. Second, the relationship between triptans in pregnancy and neurodevelopment in the child may be confounded by the underlying disease, and we do not have measures on migraine severity in MoBa. It is likely that those women continuing triptans in pregnancy have more severe migraine than those who discontinue, and as migraine is heritable[34] and associated with behavioural problems in children,[35] our results may be subject to residual confounding. We attempted to address this issue by having 2 different comparison groups, reflecting different migraine severity. If confounding by migraine severity was present, we would expect to see a stronger association for the triptans vs migraine before pregnancy only group (less severe) than for the triptans vs. migraine in pregnancy group (more severe). We observed no such trends, and a sensitivity analysis comparing children in the 2 comparison groups showed no differences in neurodevelopment. We do not have measures on migraine after birth, and it is possible that our

findings are related to differences in postnatal family environment. Besides, all outcomes are parent-reported, and reporting might vary with severity of migraine. Reporting is also likely to vary with the outcome status of the child. Further research should include more objective measures of neurodevelopment and preferably neurobehavioural diagnoses in addition to symptoms. Third, we had limited power to detect small or moderate effect sizes. This prevented us from examining specific triptans and trimesters. These limitations should be kept in mind when interpreting the results from this study.

5 | CONCLUSIONS

The current study adds to the literature on long-term effects of medications in pregnancy, and suggests that triptans do not seem to have a negative impact on behaviour problems, communication problems or temperament at 5 years of age. These findings may assist patients and clinicians when assessing the options for management of migraine during pregnancy.

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ORCID

Gerd-Marie Eskerud Harris http://orcid.org/0000-0003-3675-371X

Mollie Wood http://orcid.org/0000-0002-9302-2641

Hedvig Nordeng http://orcid.org/0000-0001-6361-2918

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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