RESEARCH ARTICLE

Association of Prenatal Exposure to Triptans, Alone or Combined With Other Migraine Medications, and Neurodevelopmental Outcomes in Offspring

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Neurology® 2025;104:e213678. doi:10.1212/WNL.0000000000213678

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Abstract

Background and Objectives

The long-term reproductive safety of migraine medications remains uncertain. This study sought to examine the effect of different intensities and durations of prenatal exposure to triptans, alone and combined with other preventive migraine medications, on neurodevelopmental disorders (NDDs) in children.

Methods

This nationwide health registry study in Norway included pregnancies of women with migraine before pregnancy and followed up their children up to 14 years of age. Single and multiple group-based trajectory models and group-based multitrajectory models were applied to cluster triptan exposure alone and combined with preventive antimigraine medications. Child outcomes, based on specialist outpatient and inpatient diagnoses, included autism spectrum and behavioral disorders, learning and intellectual disabilities, speech/language and developmental coordination disorders, and attention-deficit hyperactivity disorders (ADHDs). We fit adjusted and weighted pooled logistic regression models and standardized risk curves using propensity score–based overlap weighting.

Results

We included 26,210 pregnancies of women with migraine; 4,929 and 21,281 were, respectively, nonmedicated and medicated with triptans in the year of prepregnancy. In the latter group, we identified 4 group-based trajectories of triptans alone and combined with preventive medications: *discontinuers before* (*low use*) (41.5%, 47.0%), *early discontinuers* (*short-term low use*) (31.3%, 28.8%), *late discontinuers* (*moderate use*) (21.3%, 9.1%), and *late discontinuers* (*high use*) (5.9%, 15.2%). Overall, 1,140 children (4.3%) had a NDD (mean follow-up time: 8 years). Children born to women with any triptan trajectory had a slightly higher risk of NDD compared with children of nonmedicated women (magnitude range of the weighted hazard ratio [wHR]: 1.05–1.16). These risks decreased to the null when *discontinuers before* (*low use*) acted as a comparator (magnitude of wHR: 0.94–1.01) or when analyzing speech/language disorders or ADHD (magnitude of wHR: 0.82–1.14). There was a slightly elevated risk of autism disorders with both triptan late discontinuation trajectories (wHR 1.24, 95% CI [0.78–1.97]; wHR 1.30, 95% CI [0.66–2.56]), but the 95% CI crossed the null and the weighted risk difference remained low.

Discussion

Our findings indicate that prenatal exposure to triptans, alone or combined with other migraine medications, does not substantially increase the risk of a broad range of neurodevelopmental outcomes in children up to adolescence.

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Glossary

ADHD = attention-deficit hyperactivity disorder; **ATC** = Anatomical Therapeutic Chemical; **DDD** = defined daily dose; **GBMTM** = group-based multitrajectory model; **GBTM** = group-based trajectory model; **HR** = hazard ratio; **ICD-10** = International Classification of Diseases, 10th revision; **KUHR** = Control and Payment of Health Reimbursement Database; **LMP** = last menstrual period; **MBRN** = Medical Birth Registry of Norway; **NDD** = neurodevelopmental disorder; **NorPD** = Norwegian Prescription Database; **NPR** = Norwegian Patient Registry; **wHR** = weighted hazard ratio.

Introduction

Migraine affects most commonly women of childbearing age (population prevalence: 17%).[1,2] Disease symptoms often improve in pregnant women with preexisting migraine; nevertheless, approximately 8% experience worsening acute migraine attacks during gestation, which can lead to increased risks of both maternal and fetal complications.[3-6]

Triptans constitute a mainstay drug treatment for acute migraine attacks. The prevalence of their use is approximately 0.4% when considering the general population of pregnant women, whereas it rises to 15%–25% among pregnant migraineurs.[7-10] One study showed that only 1 in every 4 women with migraine continues triptan treatment during gestation.[11] Another study on polypharmacy in pregnant women with migraine observed that up to 26% of women used preventive medications in addition to triptans. The study also reports an increased susceptibility of these women to comorbidities such as hypertension, depression, epilepsy, and anxiety.[12] Thus, assessing the safety profile of triptans alone or combined with other migraine medications during pregnancy is challenging, given the complexity of multiple and intermittent drug use.

Previous studies have shown no substantial negative effects of prenatal triptan exposure on immediate fetal outcomes or maternal health.[13-18] Triptans cross the placenta and function by targeting serotonin receptors, thereby interfering with fetal brain and nervous system development. Yet, there is limited evidence about their potential longer term risks in offspring on the broad neurodevelopmental disorder (NDD) spectrum. Previous research primarily concentrated on a single NDD outcome measure (e.g., attention-deficit hyperactivity disorder [ADHD]) or relied on screening tools completed by parents.[19-21] Furthermore, no study investigated how the risk of NDD outcomes in children varies with different levels of prenatal exposure to triptans, either alone or in combination with other preventive migraine medications. To address these knowledge gaps, this study aimed to evaluate the association between triptan exposure trajectories during pregnancy, alone and in combination with other preventive migraine medications, and the risk of a broad and specific set of NDDs in children up to 14 years of age.

Methods

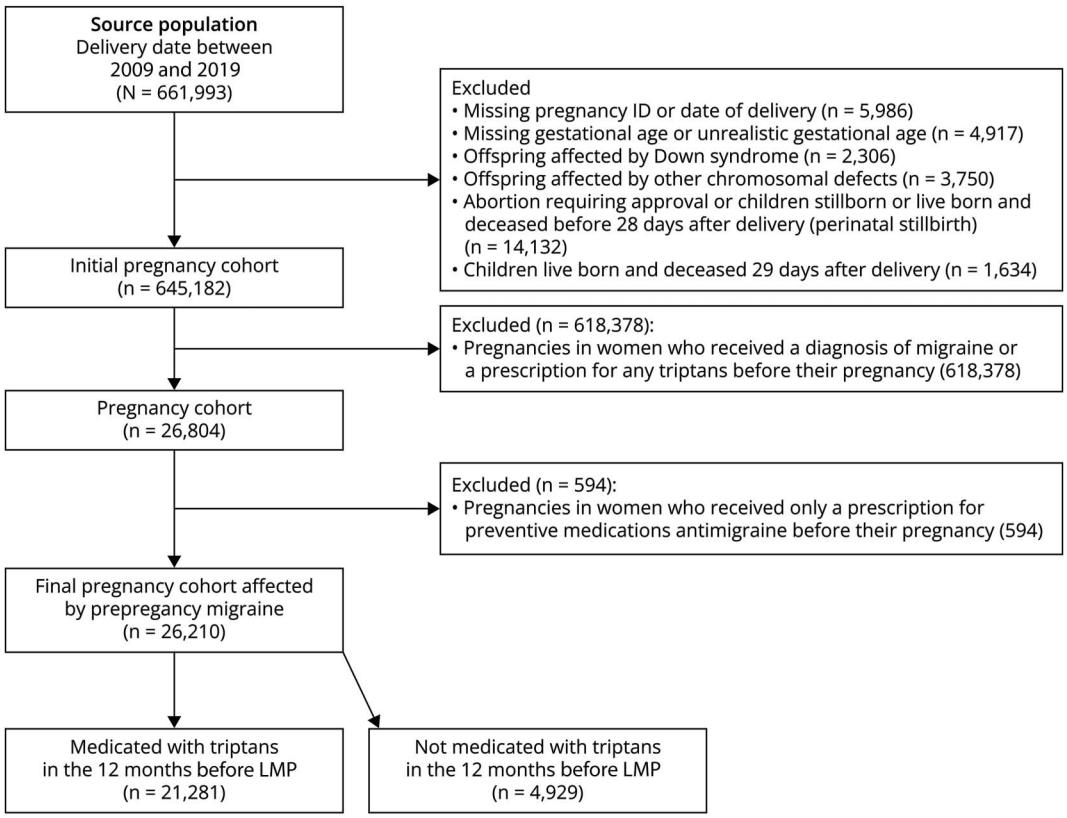
Study Design and Data Sources

In this nationwide registry-based cohort study, we linked different Norwegian health care registries for the period 2008–2023: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), the Control and Payment of Health Reimbursement Database (KUHR), and the Norwegian Patient Registry (NPR). The MBRN includes maternal and infant medical records related to pregnancy and childbirth, based on mandatory notification after 12 weeks of gestation since 1967. It provides information on gestational length (in days) ascertained through ultrasound and delivery date.[22] The last menstrual period (LMP) date is calculated by subtracting the gestational length from the delivery date. NorPD collects data on drugs dispensed by all pharmacies in Norway,[23] including the date of dispensing, the medication type according to the Anatomical Therapeutic Chemical (ATC) coding system,[24] and defined daily doses (DDDs) dispensed. NPR contains records on all inpatient and outpatient specialist encounters since 2008, including date of admission and discharge, and primary and secondary diagnoses according to the International Classification of Diseases, 10th revision (ICD-10) code system. The NPR covers all government-owned hospitals, outpatient clinics, and private health clinics that receive governmental reimbursement (where most specialized outpatient treatment in Norway is performed).[25] KUHR includes health reimbursement claims registered by general practitioners and specialists in outpatient settings since 2006, according to the ICD-10 system and the 2nd International Classification of Primary Care.[26,27]

Study Population

We included pregnancies with valid records in the MBRN (no missing IDs, date of delivery, or missing/unrealistic gestational age), having a delivery date between January 01, 2009, and December 31, 2019. Because the NPR provided data until December 31, 2022, this criterion ensured that all children had at least 3 years of follow-up data after birth. We excluded offspring with chromosomal defects, stillborn, and live-born children who died within 29 days since birth, as ascertained in the MBRN. We further limited the study population to pregnancies among women with preexisting migraine, defined as having at least one migraine diagnosis in NPR or KUHR (ICD-10: G43.X; ICPC-2: N89) and/or at least one filled triptan prescription (ATC N02CC; the indication for use is

Figure 1 Flowchart of the Study Sample*



*Conditions for exclusion can overlap with each other.

specific to migraine) within the 12 months before LMP, as performed in previous research.[28] Figure 1 shows the inclusion and exclusion criteria for identifying the final study population of pregnancy-child pairs within women with preexisting migraine (n = 26,804).

Exposure Definition

Triptan exposure from 12 months before the LMP date through the delivery date was defined as at least one filled triptan prescription within this time window for any drug belonging to the ATC group N02CC, as registered in NorPD. We defined 23 exposure intervals of 28 days each: 13 intervals before the LMP date (−364 days to LMP) and 10 intervals during pregnancy (LMP to + 280 days). We classified pregnancies to be exposed to triptans in each interval whenever a prescription was filled in the same period or if the theoretical end date of the drug supply, based on the dispensed DDDs, overlapped into the same period. The amount of triptan day supply was based on the dispensed DDDs at each prescription, assuming an average maintenance dose of 1 DDD per day. We then applied a single group-based trajectory model (GBTM) to model longitudinal exposure to triptans.

As a secondary analysis, we grouped into a single category 22 preventive migraine medications: beta-blockers, antiseizure medications, calcitonin gene-related antagonists, and other medications usually dispensed as a preventive treatment for migraine and not for attacks (eTable 1). Comparable with triptans, we defined 23 intervals of 28 days each and assessed whether intervals were covered by preventive migraine medication–filled prescriptions, assuming an average maintenance drug dose of 1 DDD per day. Next, we applied a group-based multitrajectory model (GBMTM) to examine longitudinal coexposure to triptans and other preventive migraine medications.

Outcome Definition

Because NDDs share similar mechanisms of development and symptoms and often diagnoses overlap, we explored a broad composite measure of any NDD and specific developmental traits, according to the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, fifth edition).[29] The composite NDD outcome was defined as at least one primary or secondary specialist diagnosis as registered in NPR within the child's birth date through December 31, 2022, for (1) autism spectrum disorder/pervasive developmental disorder (ICD-10 code F84.0), (2) learning disability (F81), (3) speech/language disorder (F80), (4) developmental coordination disorder (F82), (5) intellectual disability (F70-79), (6) behavioral disorder (F91), or (7) ADHD. ADHD was defined as at least one diagnostic code registered in NPR (F90) or 1 filled prescription for ADHD medications licensed

in Norway (ATC codes: C02AC02, N06BA). The specific developmental outcomes in this study included speech/language disorders, ADHD, and autism, based on study power and their higher population prevalence.

Measured Confounders

Confounders were selected based on subject knowledge and a directed acyclic graph (eFigure 1). These included the following: (1) maternal sociodemographic and lifestyle characteristics, as ascertained from the MBRN; (2) filled prescriptions of other medications in the prepregnancy year and maternal baseline comorbidities extracted from NorPD, NPR, and KUHR; (3) maternal and paternal history of any NDD (based on same ICD-10 codes as for the children in the NPR). In addition, we included a previously developed obstetric comorbidity index, adapted and measured before pregnancy.[30] More details on the confounders are given in eTable 2.

Data Analysis

To model longitudinal exposure to triptans alone or combined with preventive migraine medications, we applied a GBTM and a GBMTM, respectively, using maximum likelihood estimation and the Bernoulli distribution. We evaluated different combinations of trajectories, limiting the model selection process to three-group and four-group models with varying polynomial order (up to third order), as recommended in the literature.[31-33] We assessed model adequacy using the Bayesian information criterion, considering the highest value as the most suitable. We used clinical relevance, Bayes factors, and average posterior probability group membership of at least 0.7 for the final selection of trajectory groups.[31] We applied the "traj" plugin in Stata MP (Stata for Multiprocessing; StataCorp LLC, College Station, TX), version 17.0, with logistic models.[32]

To account for measured confounders, we used overlap weighting based on propensity score methods.[34] Logistic regression models were first fit to estimate the probability of belonging to each triptan exposure trajectory during pregnancy relative to 2 comparators: (1) the nonmedicated with triptans and (2) the triptan trajectory with the lowest exposure intensity, given the set of confounders. Then, to estimate associations between the exposure trajectories and our outcome measures, we fit an unadjusted and weighted pooled logistic regression model,[35-37] with follow-up time scaled in years since birth. We used pooled logistic regression to minimize the inherent selection bias of the Cox proportional hazard regression.[36,38] To further address confounding by migraine severity before pregnancy, we also compared the risk of the outcomes in the triptan group with lower exposure intensity vs the nonmedicated. Results are presented as hazard ratios (HRs) with 95% CIs; the HR estimates the computed odds ratio in the pooled logistic regression.[38] Next, we estimated standardized incidence risk curves by fitting the weighted pooled logistic regression models and weighted risk differences.[36] Weighted risk differences were derived to provide an absolute measure of the risk of NDD by exposure groups. Between 14% and 30% of the study population had missing data on at least one of the confounders (employment, smoking, body mass index). We performed multiple imputations by chained equations (20 imputations and 10 iterations), assuming that data were missing at random.[39,40] The imputation model included exposure and outcome variables, baseline hazard of the composite NDD outcome, and other auxiliary variables.

Sensitivity Analyses

Five sensitivity analyses were performed to assess the robustness of our results. First, we stratified the analyses by offspring sex. Next, we excluded the following from the analysis: (1) women participating with more than one pregnancy in the study; (2) women who initiated triptans during the pregnancy, thereby adopting an "as-treated" analysis; (3) children born preterm (<37 weeks of gestational age). Finally, because some behavioral disorders are mainly detected at school age, we restricted the analysis to children born before 2015 to allow at least 7 years of follow-up.

The validity of most NDD diagnoses has not been investigated for Norwegian registries. Still, previous research based on the NPR did not observe different results in subanalyses applying a stricter outcome measure definition (e.g., for ADHD, requiring a diagnostic code and filled ADHD medication prescription).[41] These data suggest an overall good validity of outcome classification in the NPR, and we did not conduct sensitivity analysis for outcome misclassification.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Regional Committee for Research Ethics in South-East Norway (approval number 85224) and by the Data Protection Officer at the University of Oslo (approval number 519858). The Regional Committee for Research Ethics in South-East Norway approved the exemption of collecting patient consent in this registry study based on automated health care databases. Data were handled and stored in accordance with the General Data Protection Regulation.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Data Availability

Relevant summary data are available within the article and/or online supporting materials. Information about individual-level data access should be directed to the individual data access providers in Norway.

Results

Of the initial eligible pregnancy cohort of 645,182 pregnancies with delivery in 2009–2019, there were 26,804 pregnancy-child pairs (4.1%) among women having migraine within 12 months before LMP. Of these, 594 were exposed only to other preventive comedications for migraine and were thereby excluded. Our final cohort included 26,210 pregnancy-child pairs in women (hereafter, "women") with migraine, where 21,281

(81.2%) were medicated with triptans within 12 months before LMP and 4,929 (18.8%) were nonmedicated with triptans in the same period (Figure 1). We identified 4 trajectories of triptan exposure from the year before pregnancy through delivery among women exposed to triptans before pregnancy (Figure 2).

1. *Discontinuers before LMP* (*low use*) (n = 8,893, 41.5%): pregnancies within women having low use of triptan before pregnancy who discontinued before LMP.
2. *Early discontinuers* (*short-term low use*) (n = 6,707, 31.3%): women who increased using triptans 6 months before LMP and who discontinued in early pregnancy.
3. *Late discontinuers* (*moderate use*) (n = 4,450, 21.3%): women with a slightly higher probability of following the therapy 12 months before conception and continuing it in early pregnancy.
4. *Late discontinuers* (*high use*) (n = 1,231, 5.9%): women who had a high probability of using triptans before and during the pregnancy.

The Table provides the distribution of baseline characteristics by exposure group. Overall, there were no considerable differences in demographic characteristics across groups. The prevalence of maternal epilepsy was higher among *late discontinuers* (*high use*) (3.7%) than in the other groups (range 1.8%–2.6% for *late discontinuers* (*moderate use*) and nonmedicated with triptans, respectively). A similar trend was observed for the use of other medications such as antidepressants, benzodiazepines, opioids, and analgesics. We used propensity score methods to minimize measured confounding. After adjusting for overlap weights, all selected covariates were balanced across the groups compared (eFigure 2).

Association of Triptan Trajectories With Neurodevelopmental Outcomes in Children

Overall, 1,140 children (4.3%) had a clinical diagnosis of any NDD, the most common being ADHD (2.5%) and speech/language disorders (1.0%). The mean follow-up time was 8.0 years (sd: 3.1), and this was similar across the exposure groups. The cumulative incidence of the NDD outcomes, overall and by trajectory groups, and children's age at first diagnoses are provided in eTables 3 and 4.

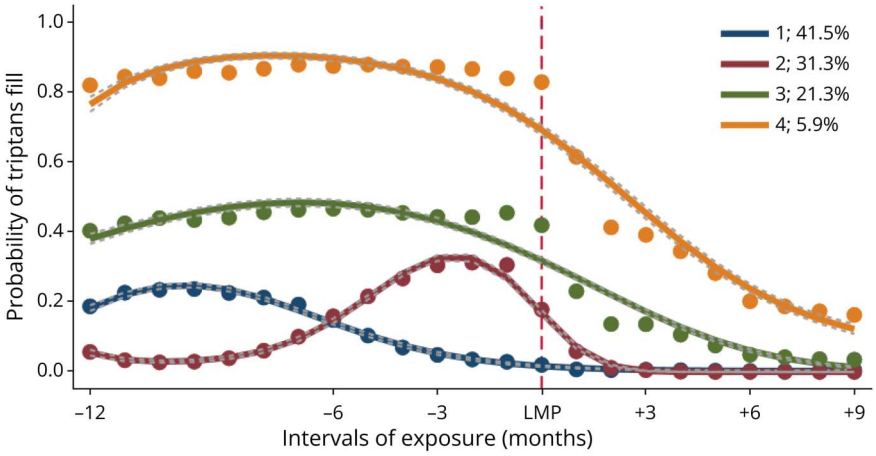
The results of the pooled logistic regression analyses are presented in Figure 3. We observed a moderately higher risk (approximately 10%) for the composite NDD outcome with all triptan trajectories (*discontinuers before* [*low use*]: weighted HR 1.08, 95% CI [0.91–1.29], *early discontinuers* [*short-term use*]: weighted HR 1.05, 95% CI [0.87–1.26], *late discontinuers* [*moderate use*]: weighted HR 1.09, 95% CI [0.88–1.36], *late discontinuers* [*high use*]: weighted HR 1.16, 95% CI [0.85–1.61]) relative to the nonmedicated group, but the 95% CIs included the null. These risks decreased to the null when *discontinuers before* (*low use*) acted as the comparator (magnitude range of the HR: 0.94–1.01). All standardized risk curves (Figure 4) showed a risk difference <1.5% for any NDD between the various triptan trajectory groups and the 2 comparators.

In analyzing the individual developmental domains (eFigures 3–8), our results for ADHD and speech disorder remained consistent with the main findings (range of weighted HR: 0.82–1.14). We observed a slightly increased risk of autism in children born to *late discontinuers* (*moderate and high use*) (weighted HR 1.24, 95% CI [0.78–1.97] and weighted HR 1.30, 95% CI [0.66–2.56], respectively). However, the 95% CI included the null, and all weighted risk differences were <1%.

Association of Multitrajectories With Neurodevelopmental Outcomes in Children

We identified 4 multitrajectories of triptans with other preventive antimigraine medications (Figure 5): *discontinuers before* (*low use*) (47.0%), *early discontinuers* (*short-term low use*) (28.8%), *late discontinuers* (*moderate use*) (9.1%), and *late discontinuers* (*high use*) (15.2%). These multitrajectories followed the same longitudinal exposure pattern as for triptans

Figure 2 Single Group-Based Trajectory Model to Cluster Triptans-Only Exposure



We named the single group-based trajectories as follows: trajectory n.1 (in blue): discontinuers before (low users); trajectory n.2 (in red): early discontinuers (short-term low users); trajectory n.3 (in green): late discontinuers (moderate users); trajectory n. 4 (in yellow): late discontinuers (high users). LMP = last menstrual period.

Table Maternal Characteristics by Triptan Trajectory Group (N = 26,210)

			Medicated with triptans							
	Nonmedicated with triptans n = 4,929		Discontinuers (low use) n = 8,893		Early discontinuers (short-term low use) n = 6,707		Late discontinuers (moderate use) n = 4,450		Late discontinuers (high use) n = 1,231	
Maternal age (mean, SD)	29.5	5.1	29.8	5.2	30.0	5.3	31.4	5.1	32.1	5.0
Prepregnancy BMI (kg/m^2)										
≤18.50	155	3.2	183	2.1	163	2.4	104	2.3	38	3.1
18.50–24.99	2,013	40.8	3,409	38.3	2,595	38.7	1,741	39.1	466	37.9
25.00–29.99	840	17.0	1,561	17.6	1,100	16.4	785	17.6	220	17.9
≥30.00	592	12.0	1,011	11.4	760	11.3	44	10.0	131	10.6
Missing	1,329	27.0	2,729	30.7	2,089	31.1	1,376	30.9	376	30.5
Parity										
Nulliparous	2,138	43.4	4,102	46.1	2,772	41.3	2,042	45.9	541	43.3
Multiparous	2,791	56.6	4,791	53.9	3,935	58.7	2,408	54.1	690	56.1
Marital status										
Married/cohabiting	4,541	92.1	8,232	92.6	6,177	92.1	4,157	93.4	1,147	93.2
Other	388	7.9	660	7.4	529	7.9	293	6.6	84	6.8
Employment status										
Employed	2,677	54.3	5,009	56.3	3,614	53.9	2,648	59.5	696	56.5
Other	1,505	30.5	2,505	28.2	1,948	29.0	1,141	25.6	352	28.6
Missing	747	15.2	1,379	15.5	1,145	17.1	661	14.9	183	14.9
Smoking before pregnancy										
Yes	639	13.0	1,144	12.9	861	12.8	493	11.1	149	12.1
Missing	632	12.8	1,233	13.9	984	14.7	654	14.7	166	13.5
Offspring sex										
Male	2,509	50.9	4,608	51.8	3,455	51.5	2,285	51.3	617	50.1
Female	2,420	49.1	4,285	48.2	3,252	48.5	2,165	48.7	614	49.9
Preterm birth	319	6.5	630	7.1	473	7.1	322	7.2	108	8.8
Year of birth										
2009–2011	859	17.4	2,434	27.4	1,746	26.0	1,084	24.4	305	24.8
2012–2014	1,460	29.6	2,356	26.5	1,759	26.2	1,163	26.1	287	23.3
2015–2017	1,574	31.9	2,439	27.4	1,881	28.0	1,253	28.2	354	28.8
2018–2019	1,036	21.0	1,664	18.7	1,321	19.7	950	21.3	285	23.2
Folic intake	3,946	80.1	7,113	80.0	5,316	79.3	3,679	82.7	1,002	81.4
ART	199	4.0	319	3.6	284	4.2	225	5.1	77	6.3
OCI (mean, SD)	0.5	0.8	0.5	0.8	0.5	0.8	0.6	0.9	0.7	1.0
Epilepsy	126	2.6	166	1.9	127	1.9	82	1.8	45	3.7
Rheumatoid arthritis	88	1.8	193	2.2	159	2.4	103	2.3	33	2.7
Depression	1,629	33.0	2,942	33.1	2,227	33.2	1,498	33.7	434	35.3
Anxiety	998	20.2	1,688	19.0	1,301	19.4	823	18.5	249	20.2

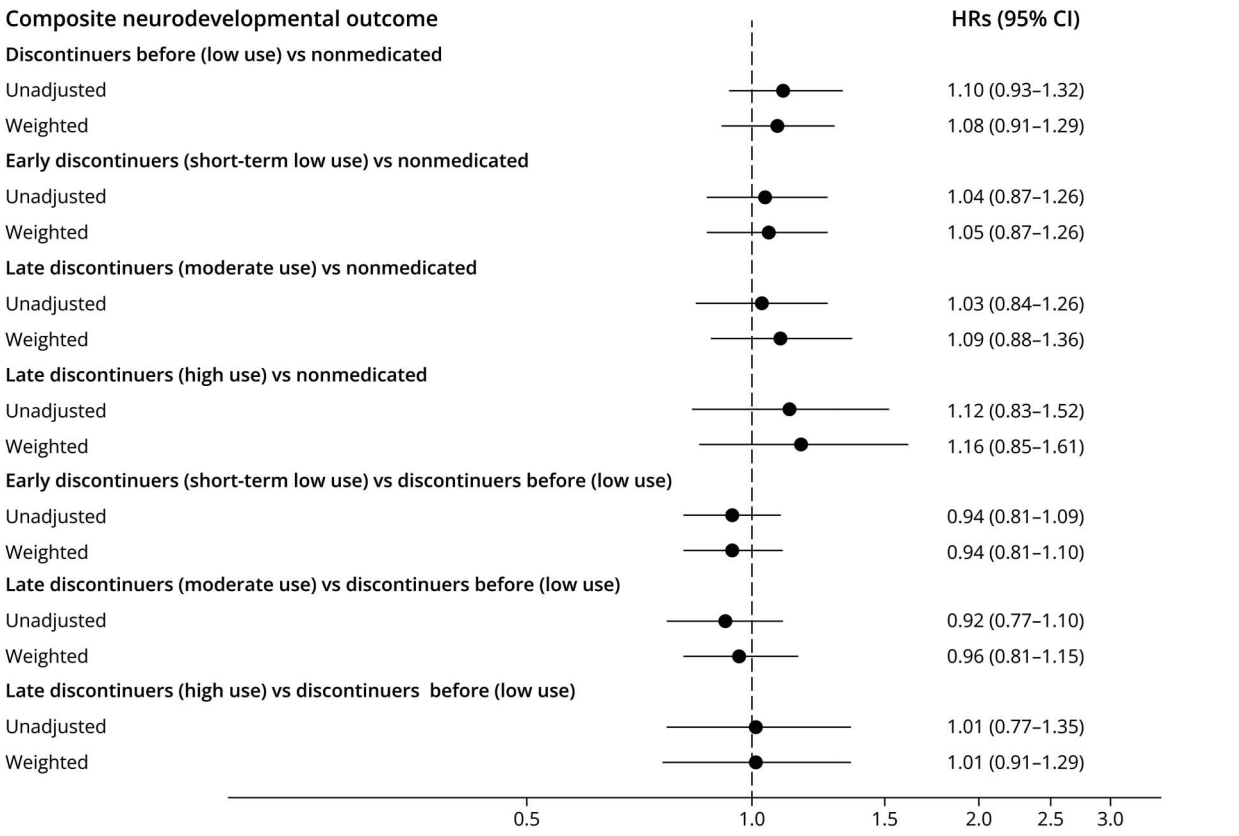
Continued

Table Maternal Characteristics by Triptan Trajectory Group (N = 26,210) *(continued)*

			Medicated with triptans							
	Nonmedicated with triptans n = 4,929		Discontinuers (low use) n = 8,893		Early discontinuers (short-term low use) n = 6,707		Late discontinuers (moderate use) n = 4,450		Late discontinuers (high use) n = 1,231	
Hypothyroidism	354	7.2	662	7.4	475	7.1	359	8.1	100	8.1
Maternal history of NDDs	66	1.3	105	1.2	64	1.0	51	1.1	14	1.1
Paternal history of NDDs	45	0.9	79	0.9	68	1.0	38	0.9	10	0.8
Comedication										
Combined hormonal contraceptives	1,170	23.7	2,647	29.8	1,752	26.1	1,138	25.6	323	26.2
Progestin-only contraceptives	651	13.2	1,208	13.6	945	14.1	676	15.2	186	15.1
Antidepressants	274	5.6	901	10.1	651	9.7	611	13.7	233	18.9
Benzodiazepines	176	3.6	420	4.7	323	4.8	266	6.0	109	8.9
Opioids	869	17.6	1,738	19.5	1,424	21.2	1,016	22.8	332	27.0
Analgesics	1,763	35.8	3,517	39.5	2,670	39.8	1,747	39.3	526	42.7
ADHD treatment	45	0.9	89	1.0	85	1.3	44	1.0	13	1.1

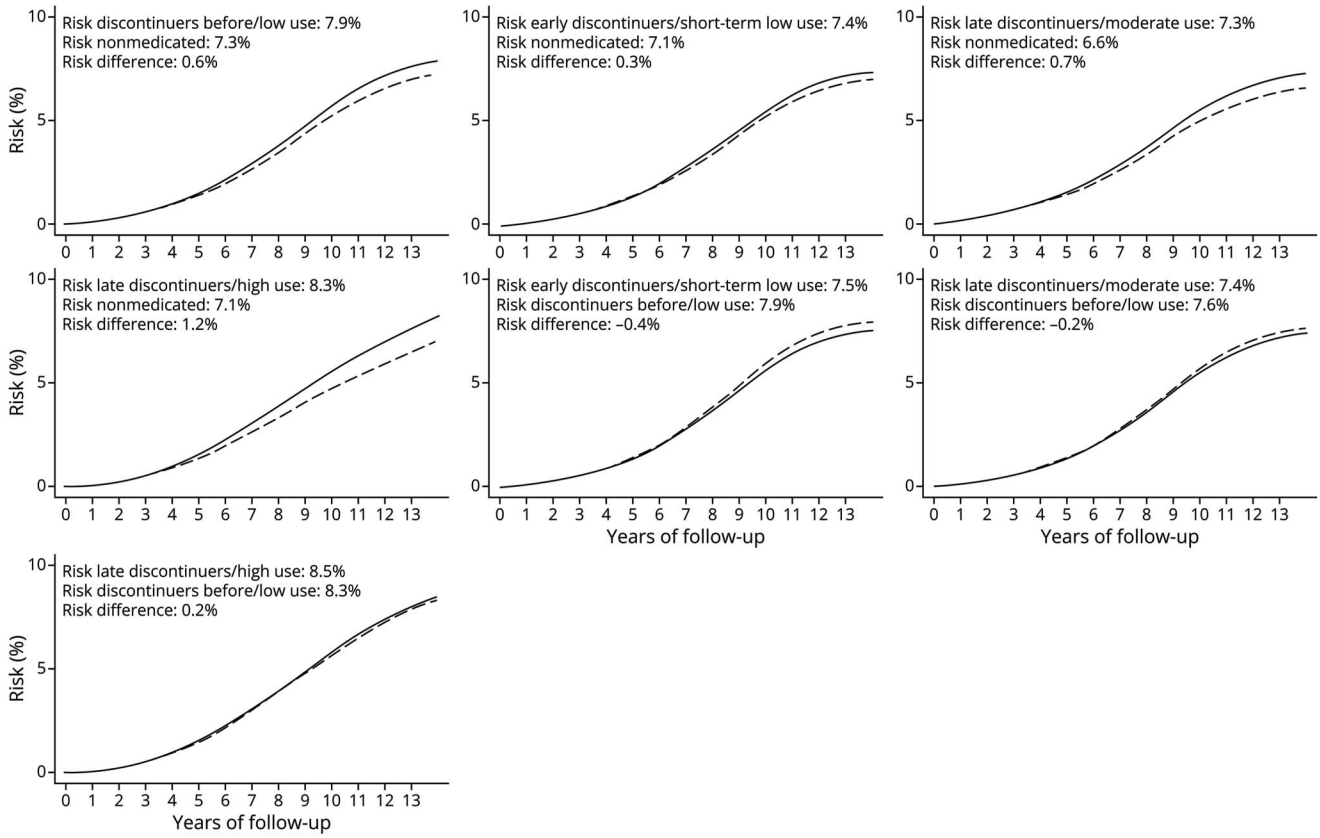
Abbreviations: ADHD = attention-deficit hyperactivity disorder; ART = assisted reproductive technology; BMI = body mass index; NDDs = neurodevelopmental disorders; OCI = obstetric comorbidity index; preterm birth = offspring born before 37 weeks of gestation.
Numbers are presented as n (%) unless otherwise indicated.

Figure 3 Crude and Adjusted Risk of NDDs in Children, According to Single Group-Based Trajectory Exposure to Triptans*



*The "nonmedicated" group comprised pregnancies within women with migraine who were unexposed to triptans in the 12 months before pregnancy start.
HR = hazard ratio; NDDs = neurodevelopmental disorders.

Figure 4 Weighted Risk Difference of NDDs in Children, According to Single Group-Based Trajectory Exposure to Triptans*



*The "nonmedicated" group comprised pregnancies within women with migraine who were unexposed to triptans in the 12 months before pregnancy start. The comparator groups ("nonmedicated" and "discontinuers before (low-use)," respectively) are represented by dashed lines while the other groups are represented by solid lines. NDDs = neurodevelopmental disorders.

alone, and the probability of using combined therapy was low (<10%). We found no association between exposure to any comedication trajectory and the composite NDD outcome in children compared with *discontinuers before* (*low use*) (weighted HRs: 0.91 [95% CI 0.79–1.06], 0.94 [95% CI 0.77–1.15], and 0.87 [95% CI 0.67–1.19] for *early discontinuers* [*short-term low use*], *late discontinuers* [*high use*], and *late discontinuers* [*moderate use*], respectively). Risk differences were <1% for all comparisons (eFigures 9–11). The risk for the specific NDD diagnoses could not be assessed because of the low sample size.

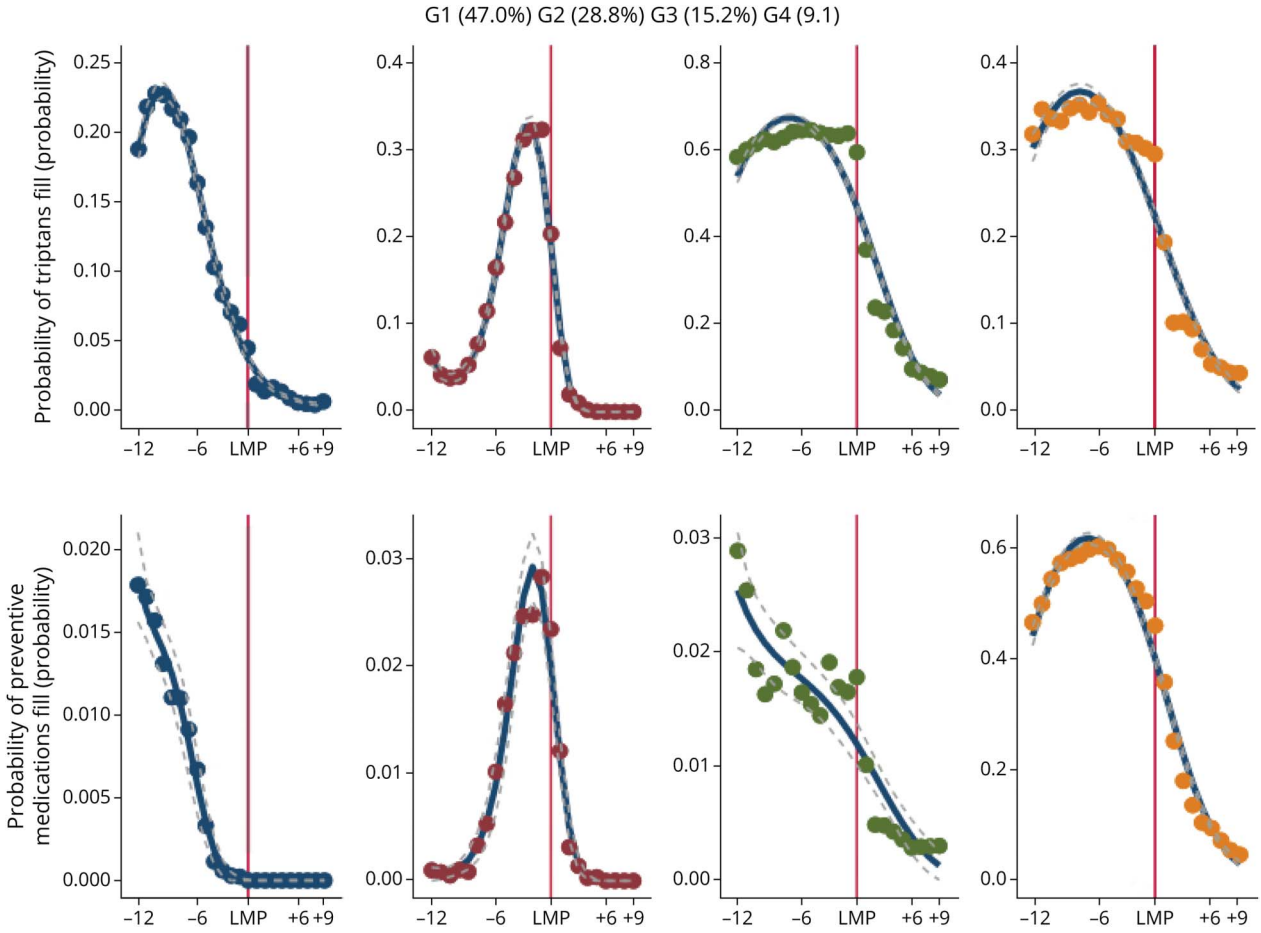
Sensitivity Analyses

eTables 5–10 provide the results of the sensitivity analyses. In the sex-specific analyses, we found no association between prenatal exposure to the various triptan trajectories and any NDD in male (range of weighted HRs: 0.96–1.17) and female (range weighted HRs: 0.81–1.27) children. Results from the analyses that excluded (1) women participating with more than one pregnancy, (2) women who initiated triptans during the pregnancy, and (3) children born before 37 weeks of gestational age were consistent with those of the main analyses. The analysis results restricted to children who reached at least the age of 7 years during the study period remained consistent with the main findings (range of weighted HRs: 0.90–1.25, and the 95% CI including the null).

Discussion

This study reports no substantial increased risk of a broad set of neurodevelopmental outcomes in children prenatally exposed to different triptan intensities and durations, either alone or in combination with other preventive medications, which is encouraging. Our study design and applied epidemiologic method limited the risk of selection bias due to the gradual decrease of susceptible children over time, as well as bias due to measured confounding. In addition, we used multiple comparison groups to minimize confounding related to migraine severity. These efforts aimed to produce the least biased effect estimates for prenatal triptan exposure and various long-term outcomes in children. Studying multiple domains of neurodevelopment is critical because it has various implications on public health costs and affects individual families and children's quality of life.[42,43] Our results contribute to the limited existing literature[9,19-21] and aid pregnant women with migraine and their health care providers in making evidence-based decisions about pharmacologic treatment with triptans and other migraine medications during gestation.

Figure 5 Multiple Group-Based Trajectory Model to Cluster Triptans and Other Preventive Antimigraine Medication Exposure



On the y-axis for each trajectory is reported the probability of triptans fill (upper part of the figure) and the probability of preventive medications fill (lower part of the figure). On the x-axis for each trajectory is reported the exposure intervals (in months). We named the multiple group-based trajectories following the same criteria as the single one: trajectory G1 (in blue): *discontinuers before* (*low users*); trajectory G2 (in red): *early discontinuers* (*short-term low users*); trajectory G3 (in yellow): *late discontinuers* (*high users*); trajectory G4 (in green): *late discontinuers* (*moderate users*). LMP = last menstrual period.

Previous research indicated a slightly greater risk of emotionality and activity problems in preschoolers prenatally exposed to triptans compared with unexposed. Still, this risk was not observed for internalizing behaviors,[19] psychomotor/communication disorders,[44] or ADHD diagnosis at a later age. These studies[9,20,21,44] used as controls women with unmedicated migraine but examined single NDD outcome measures (e.g., ADHD) or used only parent-reported screening instruments to measure child development. Notably, no previous research has assessed whether the risk of multiple NDD outcomes in offspring varied by the intensity and duration of prenatal triptan exposure. This study evaluates these aspects concurrently.

Previous studies on the reproductive long-term safety of triptans have mainly considered preschool-aged children.[9,19,21] They could have underestimated the incidence of disorders such as ADHD or learning disabilities, which mainly manifest during the school period.[43,45] Our study extended the follow-up of children up to adolescence and found no evidence of a heightened risk of ADHD, learning disabilities, or other NDDs with varying levels of prenatal exposure to triptans, either alone or combined with other preventive migraine medications. This is a clinically relevant result because many NDDs resolve spontaneously with growth, and only the most severe, typically those identified by specialists or necessitating pharmacologic interventions, are captured by registry-based studies, including our own. Previous algorithms on NDDs based on real-world data have already been validated, considering multiple diagnoses and specific observation windows for symptom onset.[45,46]

A key finding is that our weighted HRs tended to decrease to the null when the triptan *discontinuers before pregnancy* (*low use*) group, rather than the nonmedicated, acted as a comparator, except for autism. This pattern of findings across comparisons implies the important role of residual confounding by maternal migraine severity; indeed, we hypothesize that women who take triptans shortly before their LMP date and discontinue the treatment may have more severe migraine symptoms than those who do not use medications.[11,28]

Our results on individual developmental diagnoses showed that children born to *late discontinuers of triptans* (*both moderate/high use*) presented a higher risk of autism (up to 22%–30%) than their 2 comparators, albeit the 95% CI was very imprecise and included the null. Owing to the small sample size and the low prevalence of both outcome and exposure in the baseline population (0.6% in both exposed and nonmedicated children), we could not apply further stratification and triangulation methods to assess better this possible link, including sibling design to address maternal confounding by difficulties in recognition/regulation of emotions related to migraine medication overuse.[47] Nevertheless, the weighted risk differences for autism were shallow in both comparisons, confirming that the absolute measure of this risk remains low.

An important novel result is that children prenatally exposed to different intensities of triptans in combination with other preventive migraine medications presented comparable NDD risk, as a composite outcome, as their peers. Given the low extent of this prenatal coexposure in our population, we could not assess the risk of specific NDD diagnoses in children. Although few women experience very severe migraine during gestation, this group may need preventive migraine medications in addition to continued triptan treatment.[11,28] As highlighted by previous research,[12] the patterns of prenatal polypharmacy and comorbidity among women with migraine are complex and the effects of this coexposure on maternal-child health remain understudied. Our findings about the longer-term safety of multiple migraine medications during gestation need to be corroborated, or refuted, by additional studies.

This study presents multiple strengths. We included a large source population, representative of Norwegian pregnant women, and we followed up all children for at least 3 years and up to adolescence. We limited confounding by indication by restricting our sample to women with migraine before pregnancy, as advocated in previous research.[28,48] We attempted to account for potential biases due to measured confounders, missing values, and depletion of susceptible over time. Finally, we performed numerous sensitivity analyses to confirm the robustness of our results. Some limitations need to be considered when interpreting our results. Our outcome definition identified only those children with neurodevelopmental impairment that reached the threshold for a clinical diagnosis, and we could not assess the risk of developmental impairment of milder severity. By excluding perinatal deaths and congenital malformations from the initial cohort, we cannot definitively eliminate the possibility of live birth bias.[49] Confounding by other treatment indications could have affected our multitrajectory results; we cannot exclude the possibility that preventive drugs such as beta-blockers or antiepileptics were prescribed for indications other than migraine attack prevention. Furthermore, we could not assess the risk of specific NDD in children after prenatal exposure to combined migraine treatments and individual triptans because of a small sample size. We observed that most women discontinued their antimigraine medications at LMP, and we cannot verify whether discontinuation was a result of lower migraine severity. Our exposure definition was based on filled prescriptions, and we can only assume that filling a prescription corresponds to the actual intake of the migraine treatment. A previous Norwegian validation study on triptans dispensed vs self-reported demonstrated a high specificity of 95.4%, but a significantly lower sensitivity of 39.1%, indicating that studies relying solely on dispensed prescriptions may underestimate exposure to triptans.[17] Consequently, we cannot rule out the possibility of misclassification.

In this population of women with prepregnancy migraine, we found no substantial increased risk of a broad set of neurodevelopmental outcomes in children up to adolescence after prenatal triptan exposure at different intensities and durations, alone or in combination with other preventive migraine medications. Further investigations should evaluate the risk of autism in children prenatally exposed to higher triptan intensity and specific developmental outcomes after exposure to combined migraine medications, and consider potential exposure misclassification of migraine medications.

Acknowledgment

Coauthor Angela Lupattelli, PhD, died on January 21, 2025.

Author Contributions

M. Camanni: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.M.H.J. van Gelder: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A Cantarutti: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. H. Nordeng: 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. A. Lupattelli: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

Study Funding

M. Camanni was awarded a visiting scholarship by the iAPOGEE project (Norwegian Research Council, grant no. 322176) for this study.

Disclosure

A. Lupattelli is deceased; to the best of our knowledge, there are no relevant disclosures. The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® September 30, 2024. Accepted in final form April 4, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

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