Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
**eMethods.**

**Additional information about exposure**

Women could report use of medications during pregnancy in two prenatal (Q1 and Q3) and one post-partum questionnaire (Q4). In each questionnaire, women were provided with a list of different illnesses and health problems, and asked to indicate if they had the problem/illness. On the same line, they could write the name of any medication used, and indicate when it was used. Q1 covered the period six months before pregnancy and gestational week (GW) 0-4, 5-8, 9-12, and 13+. Q3 covered GW 13-16, 17-20, 21-24, 25-28, and 29+. Q4 covered the last part of pregnancy. The questionnaires are available at the Norwegian Institute of Public Health webpage: https://www.fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/.

**Additional information about statistical analyses**

Multiple imputation by chained equations was used to impute missing data in covariates, with 30 imputations. Imputation models were fitted separately for the ADHD diagnosis sample and ADHD symptoms sample, and included all covariates that were included in the weights, exposure variables and outcome variables. Treatment weights were estimated and outcome models fit in each imputed dataset, then estimates were combined. In the imputation model for ADHD diagnosis we included the hazard function, as recommended.

In the main analysis, non-overlapping regions of the propensity scores of exposed and unexposed were trimmed by excluding individuals with a propensity score outside of the common range, to avoid extrapolation. The number of individuals that were trimmed differed for each imputed dataset, but was fewer than 1% of the total ADHD diagnosis sample and fewer than 2% of the ADHD symptoms sample.

For the probabilistic bias analysis, we used trapezoidal distributions for sensitivity and specificity with 20,000 simulations. Sensitivity and specificity was assumed the same for cases and non-cases (non-differential misclassification). We were not able to identify studies reporting sensitivity and specificity for self-reported triptan use compared to interview or medication diary as gold standard. One study examined the validity of prescribed pain medication, mostly NSAIDs, and found sensitivity between 0.29-0.34 and specificity between 0.98-0.99. Recall time was longer in that study compared to this study, and we expect triptans to have higher sensitivity than NSAIDs because the indication for use is very specific. Another study reported sensitivity of 0.63 for occasional or short-term use of analgesics or antipyretics. Based on this, we defined several scenarios for the parameters of sensitivity and specificity (e.g. optimistic, realistic and pessimistic).
**eResults.**

**Additional results from sensitivity analyses**

When we restricted the ADHD symptoms analysis to children with no missing items on the Conner’s Parent Rating Scale (CPRS), results were similar to the main analysis (eTable 8).

Estimates based on trimmed and untrimmed weights were similar (eFigure 6 and 7).

Results from complete case analysis showed similarities and differences to the main analysis (eFigure 8 and 9). For ADHD symptoms, crude estimates were similar, but for the weighted estimates triptan exposed children had significantly lower scores than children whose mothers had migraine during pregnancy in the complete case analysis. However, the difference was small and not likely to be of clinical relevance.
### eTable 1. Items from the Conners’ Parent Rating Scale-Revised, Short Form (CPRS-R(S))<sup>9,10</sup> Included in Q5y

| Item | Question | Response | Chronbach’s α |
|------|----------|----------|---------------|
| 1    | Inattentive, easily distracted | 1 = Not true at all  
2 = Just a little true  
3 = Pretty much true  
4 = Very much true | 0.88 |
| 2    | Short attention span |  
| 3    | Fidgets with hands or feet, squirms in seat |  
| 4    | Messy or disorganised at home or in the kindergarten |  
| 5    | Only attends if it is something he/she is very interested in |  
| 6    | Distractibility or attention span a problem |  
| 7    | Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as activities in kindergarten or helping out at home) |  
| 8    | Gets distracted when given instructions to do something |  
| 9    | Has trouble concentrating in kindergarten |  
| 10   | Leaves seat in kindergarten or in other situations in which remaining seated is expected |  
| 11   | Does not follow through on instructions and fails to finish tasks such as putting away shoes/tidying toys (not due to oppositional behaviour or failure to understand instructions) |  
| 12   | Easily frustrated in efforts |  

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## eTable 2. Overview of Covariates

| Variable                                      | Source            | Categorization/comment                                      |
|-----------------------------------------------|-------------------|-------------------------------------------------------------|
| **Potential confounders:**                    |                   |                                                             |
| Maternal age                                  | MBRN              | Continuous                                                  |
| Marital status                                | MBRN              | Married/cohabiting or other                                  |
| Parity                                        | MBRN              | Primiparous or multiparous                                   |
| Education                                     | MoBa Q1           | College/university or other (completed or ongoing)          |
| Income                                        | MoBa Q1           | Average, low, or high                                        |
| Pre-pregnancy BMI                             | MoBa Q1           | Continuous                                                  |
| Folate intake                                 | MoBa Q1           | Yes (before/during pregnancy) or no                         |
| Smoking in early pregnancy                    | MoBa Q1           | Yes, no, or stopped                                          |
| Alcohol use in early pregnancy                | MoBa Q1           | Yes or no/minimal                                            |
| Planned pregnancy                             | MoBa Q1           | Yes or no                                                   |
| Symptoms of anxiety and depression (SCL-5)    | MoBa Q1           | Continuous (mean score)                                     |
| Maternal ADHD medication                      | NorPD             | Yes or no                                                   |
| Maternal ADHD symptoms (ASRS)                 | MoBa Q6           | Continuous (mean score)                                     |
| Satisfaction with life (SWLS)                 | MoBa Q1           | Continuous (mean score). Used as proxy for migraine severity.|
| Use of other medications during pregnancy     |                   |                                                             |
| - Paracetamol                                 | MoBa Q1, Q3, Q4   | Yes or no                                                   |
| - NSAIDs                                      |                   |                                                             |
| - Opioids                                     |                   |                                                             |
| - Preventive migraine medications             |                   |                                                             |
| - Psychotropic drugs                          |                   |                                                             |
| **Risk factors:**                             |                   |                                                             |
| Paternal ADHD medication                      | NorPD             | Yes or no                                                   |
| Child sex                                     | MBRN              | Boy or girl                                                 |
| **Possible mediators:**                       |                   |                                                             |
| Gestational hypertension                      | MBRN              | Yes or no                                                   |
| Preeclampsia                                  | MBRN              | Mild, severe, or none                                       |
| Placenta previa                               | MBRN              | Yes or no                                                   |
| Birth weight                                  | MBRN              | <2500 g or ≥2500 g                                          |
| Prematurity                                   | MBRN              | Yes (<37 weeks) or no (≥37 weeks)                          |
| Congenital malformations                      | MBRN              | Yes or no                                                   |

BMI, body mass index; MBRN, The Medical Birth Registry of Norway; NorPD, Norwegian Prescription Database; SCL-5, Symptoms Check List; ASRS, Adult ADHD Self-Report Scale; SWLS, Satisfaction With Life Scale
**eTable 3. Characteristics of Weights Using Different Model Specifications**

| Model specification                                                                 | Estimated IPTW (ADHD diagnosis) | Estimated IPTW*IPCW (ADHD symptoms) |
|-------------------------------------------------------------------------------------|---------------------------------|-------------------------------------|
| Triptan exposed vs. migraine in pregnancy                                           |                                 |                                     |
| Main model: All potential confounders and risk factors for the outcome              | 1.0 (0.18) 0.25-4.0             | 1.0 (0.38) 0.25-5.1                 |
| Alternative model 1: Including maternal ADHD symptoms                              | 1.0 (0.18) 0.25-4.2             | 1.0 (0.38) 0.25-5.3                 |
| Alternative model 2: Not including paternal and child factors                       | 1.0 (0.18) 0.26-3.7             | 1.0 (0.37) 0.25-5.3                 |
| Alternative model 3: Including prematurity and low birth weight (considering them as risk factors rather than mediators) | 1.0 (0.18) 0.25-3.5             | 1.0 (0.37) 0.25-5.2                 |
| Triptan exposed vs. migraine before pregnancy                                       |                                 |                                     |
| Main model: All potential confounders and risk factors for the outcome              | 1.0 (0.25) 0.16-6.3             | 1.0 (0.42) 0.19-9.0                 |
| Alternative model 1: Including maternal ADHD symptoms                              | 1.0 (0.26) 0.15-7.0             | 1.0 (0.40) 0.19-8.6                 |
| Alternative model 2: Not including paternal and child factors                       | 1.0 (0.26) 0.16-6.5             | 1.0 (0.41) 0.19-9.0                 |
| Alternative model 3: Including prematurity and low birth weight (considering them as risk factors rather than mediators) | 1.0 (0.25) 0.16-6.6             | 1.0 (0.43) 0.18-9.1                 |

IPTW, Inverse Probability of Treatment Weight, IPCW; Inverse Probability of Censoring Weight
eTable 4. CPRS Score According to ADHD Diagnosis

| ADHD diagnosis | No  | Mean score (SD) | Mean z-score (SD) |
|----------------|-----|-----------------|-------------------|
| Yes            | 115 | 2.01 (0.75)     | 1.69 (1.94)       |
| No             | 4252| 1.38 (0.39)     | 0.03 (1.01)       |

CPRS; Conners Parent Rating Scale; SD, standard deviation; CI, confidence interval
### eTable 5. Probabilistic Bias Analysis of Non-Differential Misclassification of Exposure in the Weighted ADHD Diagnosis Analysis, Using Trapezoidal Distributions for Sensitivities and Specificities According to Different Scenarios

|                  | Sensitivity | Specificity | Corrected estimate\(^a\), RR (95% CI) | Bias\(^b\), % |
|------------------|-------------|-------------|----------------------------------------|---------------|
|                  | Min M1 M2 Max | Min M1 M2 Max |                                      |               |
| Optimistic       |             |             |                                        |               |
| scenario 1       | 0.70 0.75 0.85 1.0 | 0.95 0.98 0.99 1.0 | 1.04 (0.70, 1.53) | 1.0           |
| Optimistic       |             |             |                                        |               |
| scenario 2       | 0.70 0.75 0.80 0.85 | 0.95 0.98 0.99 1.0 | 1.04 (0.70, 1.53) | 1.0           |
| Realistic        |             |             |                                        |               |
| scenario 1       | 0.30 0.60 0.70 0.90 | 0.90 0.95 0.98 1.0 | 1.05 (0.71, 1.54) | 1.9           |
| Realistic        |             |             |                                        |               |
| scenario 2       | 0.50 0.60 0.70 0.80 | 0.90 0.92 0.95 0.97 | 1.05 (0.71, 1.55) | 1.9           |
| Pessimistic      |             |             |                                        |               |
| scenario 1       | 0.15 0.20 0.30 0.50 | 0.70 0.80 0.90 1.0 | 1.20 (0.77, 3.40) | 14.2          |
| Pessimistic      |             |             |                                        |               |
| scenario 2       | 0.30 0.40 0.50 0.60 | 0.70 0.80 0.85 0.90 | 1.31 (0.82, 5.95) | 21.4          |
| Pessimistic      |             |             |                                        |               |
| scenario 3       | 0.30 0.40 0.50 0.60 | 0.60 0.70 0.80 0.85 | 2.09 (1.10, 17.9) | 50.7          |

\(^a\)Median bias-adjusted estimate with 95% simulation limits. \(^b\)Calculated as ((corrected-conventional)/corrected)*100

Conventional estimate = 1.03 (0.69-1.51). Migraine during pregnancy was used as comparison group.

M, mode; RR, rate ratio; CI, confidence interval.
**eTable 6.** Associations Between Prenatal Triptan Exposure and Child ADHD Diagnosis Using Only Data From NPR to Assess ADHD Diagnosis and Restricting to Children Born in or After 2008

|                          | No  | ADHD cases, No | IR per 1000 person-years (95% CI) | Crude HR (95% CI) | Weighted HR (95% CI) |
|--------------------------|-----|----------------|-----------------------------------|------------------|---------------------|
| Triptans in pregnancy    | 132 | 2              | 1.9 (0.5, 7.8)                    | 1.67 (0.34, 8.22) | 1.45 (0.30, 7.22)   |
| Migraine in pregnancy    | 657 | 6              | 1.2 (0.5, 2.6)                    | 1 (reference)     | 1 (reference)       |
| Triptans in pregnancy    | 132 | 2              | 1.9 (0.5, 7.8)                    | -                | -                   |
| Migraine prior to pregnancy | 955 | 7              | 0.9 (0.4, 2.0)                    | -                | -                   |

IR, incidence rate; HR, hazard ratio; CI, confidence interval
**eTable 7. Associations Between Prenatal Triptan Exposure and Child ADHD Symptoms, Restricted to Children With no Missing Items on the CPRS**

| No | Mean CPRS score (SD) | Mean CPRS z-score (SD) | Crude mean difference in z-scores^a (95% CI) | Weighted mean difference in z-scores^a (95% CI) |
|----|----------------------|------------------------|------------------------------------------|---------------------------------------------|
| Triptans in pregnancy | 388 | 1.37 (0.39) | 0.00 (1.03) | -0.05 (-0.17, 0.07) | -0.11 (-0.25, 0.03) |
| Migraine in pregnancy | 1609 | 1.39 (0.42) | 0.05 (1.11) | 0 (reference) | 0 (reference) |
| Triptans in pregnancy | 388 | 1.37 (1.39) | 0.00 (1.03) | -0.07 (-0.18, 0.05) | -0.07 (0.23, 0.09) |
| Migraine prior to pregnancy | 2197 | 1.39 (0.40) | 0.07 (1.05) | 0 (reference) | 0 (reference) |

CPRS; Conners Parent Rating Scale; SD, standard deviation; CI, confidence interval
eFigure 1. Measures of ADHD According to Data Source and Time Coverage

*Not including modafinil
eFigure 2. Proposed Causal Model for the Association Between Triptan Use During Pregnancy and Child ADHD

Socioeconomic status (SES) includes education and income. Neonatal complications include congenital malformations, preterm birth and low birthweight. Obstetric complications include gestational hypertension, preeclampsia and placenta previa. Biasing paths in pink; causal paths in green. The figure was made using www.dagitty.net.
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eReferences.

1. Norwegian Mother, Father and Child Cohort Study (MoBa): Questionnaires from MoBa. The Norwegian Institute of Public Health. https://www.fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/. Published 2005. Updated 2021. Accessed January 10, 2022.
2. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
3. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-399.
4. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. Stat Med. 2019;38(26):5120-5132.
5. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med. 2009;28(15):1982-1998.
6. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. Am J Epidemiol. 2010;172(7):843-854.
7. van Gelder MM, van Rooij IA, de Walle HE, Roeleveld N, Bakker MK. Maternal recall of prescription medication use during pregnancy using a paper-based questionnaire: a validation study in the Netherlands. Drug Saf. 2013;36(1):43-54.
8. van Gelder M, Vorstenbosch S, Te Winkel B, van Puijenbroek EP, Roeleveld N. Using Web-Based Questionnaires to Assess Medication Use During Pregnancy: A Validation Study in 2 Prospectively Enrolled Cohorts. Am J Epidemiol. 2018;187(2):326-336.
9. Kumar G, Steer RA. Factorial validity of the Conners' Parent Rating Scale-revised: short form with psychiatric outpatients. J Pers Assess. 2003;80(3):252-259.
10. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol. 1998;26(4):257-268.