1 **Prenatal triptan exposure and neurodevelopmental outcomes**

2 **in 5-year-old children: follow-up from The Norwegian Mother**

3 **and Child Cohort Study**

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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 externalizing behavior problems in toddlers exposed to triptans during pregnancy

Methods: We included 3 784 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, 1 509 (39.9%) reported migraine during pregnancy but no triptan use, and 1 922 (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 internalizing and externalizing behavior, 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 behavior or communication problems.

Conclusions: Contrary to results from previous studies in younger children, we found no increased risk of externalizing behavior 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.

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 behavior 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 anti-migraine 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 externalizing behavior in triptan-exposed children at 3 years, compared to migraine controls (RR 1.36, 95% CI [1.02, 1.81]), but no increased risk of internalizing behavior.[12] The increased rates of externalizing behavior 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

64 exposure after adjusting for migraine severity.[14] The association between triptan exposure in pregnancy

65 and child neurodevelopment has not been examined in other studies.

66 Following these studies, our aim was to investigate the association between triptan exposure in

67 pregnancy and externalizing behavior, internalizing behavior, communication and temperament in 5-year-

68 old children in the MoBa, using psychometric instruments that are internationally recognized in the field

69 of psychology to assess these traits.

70 **Methods**

71 Population and data collection

72 This study used data from the Norwegian Mother and Child Cohort Study (MoBa), linked to the Medical

73 Birth Registry of Norway (MBRN) (Data Version 9, released November 2015). MoBa is a prospective

74 population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health that

75 includes data on over 100 000 mother-child pairs.[15] All women in Norway who were pregnant between

76 1999 and 2008 received a postal invitation to participate prior to their routine ultrasound examination in

77 gestational week 17-18. The initial participation rate was 41%. Mothers younger than 25 years, those

78 living alone, mothers with more than two previous births, mothers with previous stillbirth, and smokers

79 were underrepresented; and mothers taking folate supplements and multivitamins were overrepresented.[16]

80 Follow-up is conducted via questionnaires in pregnancy weeks 17, 22 and 30, and at child's age 6 and 18

81 months, 3 and 5 years, and onward. Using each participant's personal identification number, the MoBa

82 data is linked to the MBRN, which includes information on pregnancy, delivery, and the health of the

83 neonate for all births in Norway.[17]

84 For the current study, we required women to have completed the questionnaires with information on

85 medication exposure in pregnancy (Q1, Q3 and Q4), as well as the questionnaire at child age 5 years (Q5y).

86 A total of 90.7% of the women who originally consented completed Q1. Of those, 91.3% also completed Q3,

87 and 90.0% completed Q4. Q5y was returned by 45.7% of these women. As this study focused on

88 neurodevelopment, we excluded infants not born alive. Women with undefined exposure (i.e. reported

89 migraine and indicated that a drug was taken, but not which drug) or with unknown triptan timing (reported

90 triptan use, but not whether it was used before or during pregnancy) were also excluded, as well as twins

91 and triplets. Women with unknown triptan timing during pregnancy were included. An overview of drop-

92 out and exclusion criteria is presented in Figure 1. The analytic sample consisted of 37 656 children whose

93 mothers completed Q5y, of which 2 697 (7.2%) had missing covariates and were excluded. In the remaining

94 complete case sample of 34 959 children, 3 784 (10.8%) of the mothers reported to have migraine.

95 Triptan exposure

96 Medication use in pregnancy was reported in Q1 (6 months pre-pregnancy and gestational weeks 0-13+),

97 Q3 (week 13-29+) and Q4 (week 30-end of pregnancy) for specific indications. Drug exposure was coded

98 in groups based on the Anatomical Therapeutic Chemical (ATC) Classification System.[18] The exposed

99 group included children of women who reported use of triptans in pregnancy, defined as reporting of

100 ATC code N02CC under any of the indications that were mentioned in the questionnaires, as triptans are

101 used exclusively for migraine. In the first questionnaire, women could report if they had migraine before

102 and/or during pregnancy. Based on this information, we defined two non-exposed comparison groups; (a)

103 children whose mothers reported migraine in pregnancy that were not treated with triptans, and (b)

104 children of mothers who reported migraine before pregnancy only, as shown in Figure 1. When studying

105 long-term outcomes such as neurodevelopment, triptan exposure during the entire pregnancy is

106 etiologically relevant.

107 Neurodevelopmental outcomes

108 The Child Behavior Checklist (CBCL) is a widely used method of identifying behavioral and emotional

109 problems in children. A short version was used in the MoBa.[19] We included the externalizing domain

110 (consisting of the subscales 'attention problems' and 'aggressive behavior') and the internalizing domain

111 (consisting of the subscales 'emotionally reactive', 'anxious/depressed', and 'somatic complaints').

112   Clinically significant externalizing behavior problems and internalizing behavior problems were defined

113   as T-scores of 63 or greater, as recommended.[20]

114   The Ages and Stages Questionnaire (ASQ) is a screening tool used to detect developmental delays in

115   five domains; however, the five-year questionnaire in the MoBa only includes the communication domain,

116   which has seven questions regarding the child's language competence.[21] Communication problems were

117   defined as children with T-scores of 65 or greater.[22]

118   The Emotionality Activity and Shyness Temperament Questionnaire (EAS) measures four temperament

119   traits: emotionality (the tendency to become emotionally aroused easily and intensely), activity (preferred

120   activity level), sociability (the tendency to prefer the presence of others to being alone) and shyness (the

121   tendency to be awkward and inhibited in new social situations).[23] The short version used in the MoBa

122   includes 12 statements, three in each domain.[24] As these are temperament traits, akin to normal

123   personality in adults, there is no recommended cut-off. Higher T-scores indicate children who are more

124   emotional, more active etc., relative to other children in the sample.

125   Additional information about scoring and items comprising the scales can be found in the

126   supplementary material.

Covariates

128   Potential confounders and risk factors for the outcomes were identified through literature review and

129   directed acyclic graphs (DAGs)[25] (Supplementary Figure 1). All covariates were categorized as presented

130   in Table 1. Information on maternal age at delivery, marital status, parity, pregnancy complications

131   (gestational diabetes and hypertensive disorders), child sex, birthweight, gestational age, and

132   malformations was obtained from the MBRN. Highest level of completed and ongoing education, body

133   mass index (BMI) before conception, folate intake before and during pregnancy (four weeks prior to

134   pregnancy and/or until week 12 in pregnancy), concomitant medication use, smoking habits, alcohol

135   intake, and symptoms of depression or anxiety were self-reported in the MoBa questionnaires. An

136   overview of the sources of the covariates can be found in Supplementary Figure 2.

137   Symptoms of depression/anxiety were measured by a short version of the Hopkins Symptoms Checklist

138   (SCL-5)[26] twice during pregnancy, and mean scores at each time point were standardized. Alcohol intake

139   in pregnancy was classified as "No or minimal" (less than once per month), "Moderate" (once per month

140   to once per week) and "Frequent" (more than once per week). Relevant co-medications were the

141   following: analgesics in the ATC groups M01A (NSAIDs), N02BE01 (paracetamol), N02A (opioids);

142   psychotropic drugs in ATC groups N05A (antipsychotics), N05BA (benzodiazepines), N05CF

143   (benzodiazepine-like), N06A (antidepressants), N06BA (stimulants); and preventive migraine therapy in

144   groups N06AA (tricyclic antidepressants), N03A (antiepileptic's), C07A (beta blockers), C09A (ACE-

145   inhibitors), C09C (AII-blockers) and M03AX (botulinum toxin).

146   Statistical analysis

147   We first determined the characteristics of women and children in the migraine sample, according to

148   exposure group. In order to account for differences in the characteristics of women using triptans in

149   pregnancy and those who did not, we used propensity score based methods with inverse probability of

150   treatment weights (IPTW).[27] Using logistic regression, we calculated the probability of taking triptans in

151   pregnancy compared to (a) having migraine not treated with triptans, and (b) having migraine prior to

152   pregnancy only, conditional on age, parity, education, marital status, pre-pregnancy BMI, concomitant

153   medication use, mean SCL5-score, smoking, alcohol, folate intake, and child sex. We used the propensity

154   scores to calculate stabilized IPTW, and checked that the covariates were sufficiently balanced between

155   the exposed/unexposed groups; standardized differences less than 0.1 were considered acceptable.[27] In

156   addition, stabilized inverse probability of censoring weights (IPCW) were estimated for each outcome in

157   order to account for dropout at 5 years, up-weighting the women who remain to represent similar women

158   who drop out.[28] These weights included the same variables as in the IPTW models, except smoking and

159   alcohol, as models including these covariates resulted in extreme weights. We fit outcome models with

160   the combined weights (IPTW multiplied by IPCW), using negative log-binomial regression for

161   categorical outcomes (CBCL and ASQ), and linear regression for continuous outcomes (EAS). Robust

162   variance estimation was applied to account for the weights.[27] The outcome models included children with

163   complete outcome information, except for ASQ, where we also included those with one missing item out

164   of the seven included in the communication scale. We conducted an a-priori sample size analysis in order

165   to estimate detectable effect sizes, as described more detailed in the supplementary material.

166   We performed several sensitivity analyses. First, we repeated our main analysis in children whose

167   mothers did not use paracetamol during pregnancy, in order to address potential residual confounding by

168   paracetamol exposure. Second, we used probabilistic bias analysis to quantify the potential impact of

169   selection bias from loss to follow-up.[29] We estimated associations between loss to follow-up and

170   externalizing behavior problems by using selection proportions that we considered reasonable based on

171   data at 3 years. For the probabilistic analysis we used a trapezoidal distribution of the selection odds ratios

172   with 10 000 simulations. Third, we did an analysis comparing the two unexposed groups (children of

173   women with migraine during pregnancy versus children of women with migraine prior to pregnancy only)

174   to look for differences in neurodevelopment related to active untreated migraine. Fourth, we modeled

175   externalizing and internalizing behaviors and communication as continuous outcomes in order to better be

176   able to pick up small but potentially meaningful differences in these outcomes.

177   Stata MP Version 14.1 was used in all analyses.

178   **Results**

179   Description of the study sample

180   Of the 3 784 women with migraine, 353 (9.3%) reported use of triptans during pregnancy, 1 509 (39.9%)

181   reported migraine in pregnancy but no use of triptans, and 1 922 (50.8%) had migraine before pregnancy

182   only. The most commonly used triptan was sumatriptan (Supplementary Table 1). Maternal and child

183   characteristics in the three groups before and after weighting are presented in Table 1. Women in the

184   exposed group were slightly older than women in the comparison groups , and they were more likely to

185   be first time mothers compared to women with migraine in pregnancy not treated with triptans, but less

likely to be first time mothers compared to women with migraine prior to pregnancy only. There was little difference in other socio-demographic 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 Supplementary Table 2). 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 Supplementary Table 3, including the amount of missingness for each covariate. Responses to all items on the CBCL and EAS, and at least six out of seven items on the ASQ communication scale, were available for over 96% of the children in the migraine sample. For ASQ, 10.5% were missing one item on the communication scale, and these children were included in the analysis.

Neurodevelopmental outcomes

We found no increased risk of externalizing behavior problems associated with triptan exposure in fetal life. In fact, we observed a lower risk of externalizing problems for triptan exposed children compared to 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 (Supplementary Table 4).

Sensitivity analyses

209 Sensitivity analyses excluding women who used paracetamol revealed similarities and differences to the

210 main analysis (Supplementary Table 7 and 8). Most estimates in the restricted sample fell within the 95%

211 confidence interval of the estimates from the main analysis, with the exception of sociability. An

212 additional analysis comparing the two comparison groups showed no differences in neurodevelopment

213 between children of women with migraine in pregnancy and children of women with migraine before

214 pregnancy only (results not shown). As a further analysis to quantify the sensitivity of our finding for

215 externalizing behavior problems to selection bias, we conducted a probabilistic bias analysis with

216 selection associations based on the results in Supplementary Table 6. We observed a corrected OR of 0.60

217 with a 95% confidence interval ranging from 0.46 to 0.89, compared to the conventional OR 0.67, 95%

218 CI [0.43, 1.04]. When modeling externalizing and internalizing behaviors and communication as

219 continuous outcomes, we observed findings consistent with the results of the main analysis. In particular,

220 this analysis supported the trend towards a lower risk of externalizing problems observed in the main

221 analysis, as children exposed to triptans demonstrated slightly lower mean scores on the externalizing

222 behavior scale compared to children in both comparison groups (Supplementary Table 10).

223 **Comment**

224 Principal findings

225 In this study of 3 784 pregnant women with migraine and their children at 5 years of age, we found no

226 increased risk of behavior problems (internalizing and externalizing) or communication problems

227 following prenatal triptan exposure. Rather, the risk of externalizing behavior problems seemed to be

228 lower in the triptan exposed children. Triptan exposed children also scored higher on the sociability trait

229 compared to unexposed children whose mothers had migraine during pregnancy, but not compared to

230 children whose mothers had migraine prior to pregnancy only. We found no differences for other

231 temperament traits (activity, emotionality, and shyness).

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 to 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 externalizing behavior 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 three years may have resolved by age five, suggesting the triptan exposure results in early, but not persistent, behavior problems. Second, 3-year-old children with externalizing problems were less likely to be present at 5 years (53%) compared to 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 internalizing

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257 behavior or communication problems associated with prenatal triptan exposure,[12,14] which is in line with

258 our findings in 5-year-olds.

Strengths of the study

260 This study has several important strengths. MoBa is one of the largest population-based cohorts

261 worldwide, following almost 40 000 pregnant women and their children until the age of 5. The

262 prospective design and long follow-up allowed us to investigate potential long-term effects of

263 medications in pregnancy, which is an important public health perspective given the increasing

264 prevalence and burden of neurodevelopmental and psychiatric disorders in children.[32,33] Extensive

265 information on neurodevelopment made it possible to examine several relevant outcomes, using

266 established, well-validated psychometric instruments.[19,21,24] Furthermore, detailed information on a

267 variety of characteristics were available in MoBa, including maternal socio-demographic and life style

268 factors, mental health, and drug use, which are potential confounders for the relationship between triptan

269 use in pregnancy and later neurodevelopmental problems in the child.

Limitations of the data

271 There are also several limitations to consider. Firstly, selection bias arising from loss to follow-up is a

272 concern in MoBa as well as in other population-based cohort studies. Even though we used IPCW to up-

273 weight women who remain in the sample to represent similar women who drop out, we cannot rule out

274 that selection bias might have affected our results: there could be unknown or unmeasured predictors of

275 drop-out, such as migraine severity or genetic vulnerability. This should be kept in mind, along with the

276 fact that neurodevelopmental problems in themselves also could be driving drop-out, as discussed.

277 However, as shown in our probabilistic analysis, this is not likely to fully explain the findings. Secondly,

278 the relationship between triptans in pregnancy and neurodevelopment in the child may be confounded by

279 the underlying disease, and we do not have measures on migraine severity in MoBa. It is likely that those

280 women continuing triptans in pregnancy have more severe migraine than those who discontinue, and as

281   migraine is heritable[34] and associated with behavioral problems in children[35], our results may be subject to

282   residual confounding. We attempted to address this issue by having two different comparison groups,

283   reflecting different migraine severity. If confounding by migraine severity was present, we would expect

284   to see a stronger association for the triptans vs. migraine before pregnancy only group (less severe) than

285   for the triptans vs. migraine in pregnancy group (more severe). We observed no such trends, and a

286   sensitivity analysis comparing children in the two comparison groups showed no differences in

287   neurodevelopment. We do not have measures on migraine after birth, and it is possible that our findings

288   are related to differences in post-natal family environment. Besides, all outcomes are parent-reported, and

289   reporting might vary with severity of migraine. Reporting is also likely to vary with the outcome status of

290   the child. Further research should include more objective measures of neurodevelopment and preferably

291   neurobehavioral diagnoses in addition to symptoms. Third, we had limited power to detect small or

292   moderate effect sizes. This prevented us from examining specific triptans and trimesters. These

293   limitations should be kept in mind when interpreting the results from this study.

294   Conclusions

295   The current study adds to the literature on long-term effects of medications in pregnancy, and suggests

296   that triptans do not seem to have a negative impact on behavior problems, communication problems or

297   temperament at 5 years of age. These findings may assist patients and clinicians when assessing the

298   options for management of migraine during pregnancy.

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Figure legends

Figure 1. Overview of the study sample

Supporting Information

Supplementary Figure 1. Possible directed acyclic graph (DAG) for the association between triptans in pregnancy and neurodevelopment in the child

Supplementary Figure 2. Overview of the sources of the relevant variables in the MoBa and MBRN

Supplementary Table 1. Use of specific triptans before and during pregnancy

Supplementary Table 2. Overview of relevant co-medications in pregnancy

Supplementary Table 3. Characteristics of the complete case sample and the full cohort

Supplementary Table 4. Power analysis

Supplementary Table 5. Characteristics of generated stabilized weights

Supplementary Table 6. Bias analysis for the potential impact of selection bias due to loss-to-follow up on observed effect estimates for externalizing behavior

Supplementary Table 7. Associations of exposure to triptans in pregnancy with behavior and communication in restricted sample

Supplementary Table 8. Associations of exposure to triptans in pregnancy with temperament in restricted sample

Supplementary Table 9. Sub-scale reliability (Chronbach's α) and items composing CBCL, ASQ and EAS in MoBa Q5y

Supplementary Table 10. Associations of exposure to triptans in pregnancy with externalizing and internalizing behaviors and communication (continuous measures)
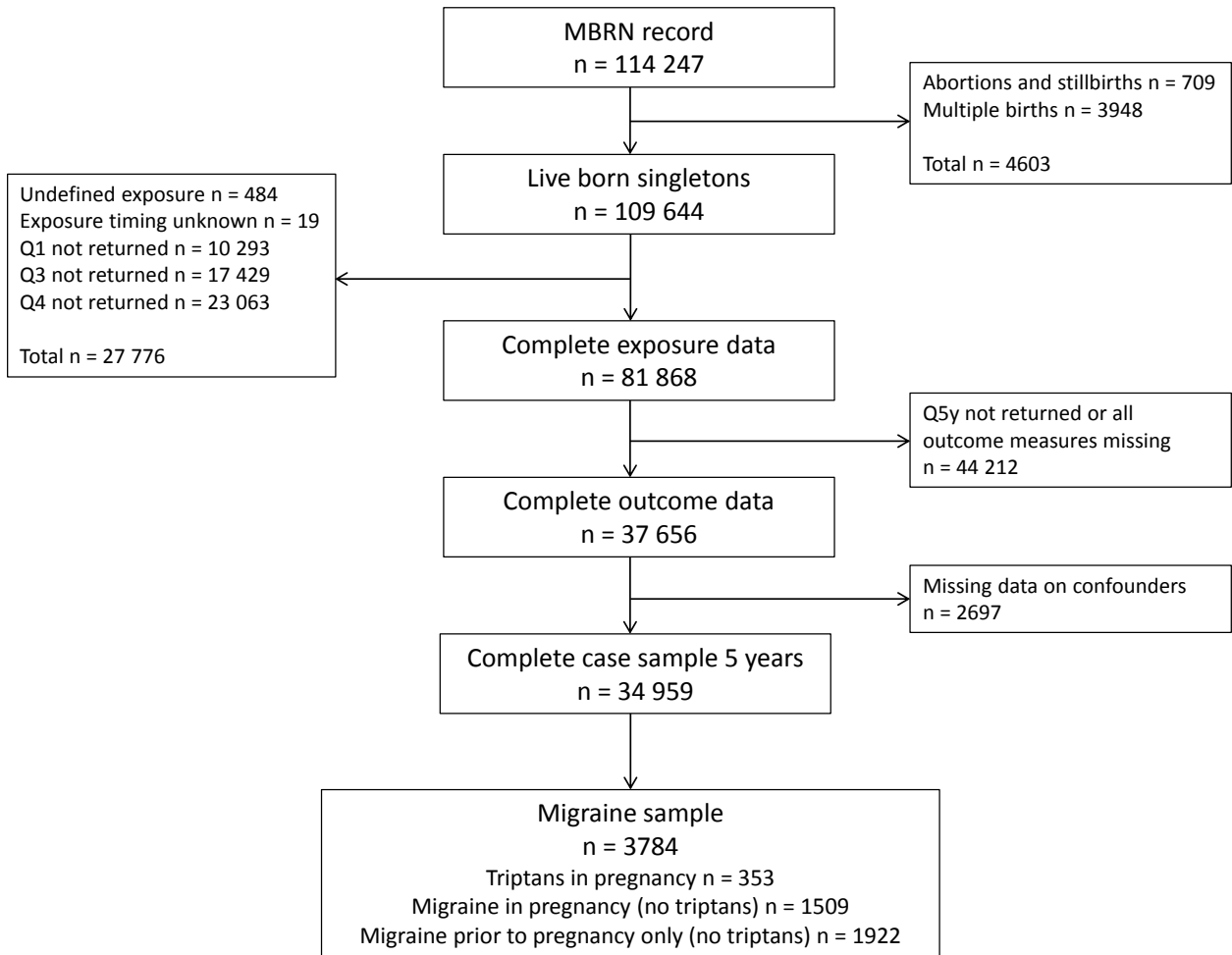
Table 1. Baseline characteristics before and after IPT weighting in exposed and unexposed groups

	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=1 509	Exp. n=353	Unexp. n=1 509	Exp. n=353	Unexp. n=1 922	Exp. n=353	Unexp. n=1 922
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 anti-migraine 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] Standardized differences above 0.1

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

[d] Not included in IPT weighting based on DAG

Table 2. Associations of exposure to triptans in pregnancy with behavior and communication at 5 years of age

	Total number, n	Number with outcome, % of n	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Child Behavior Checklist:				
Externalizing problems				
Triptans in pregnancy	340	7.4	0.69 (0.46, 1.04)	0.68 (0.44, 1.05)
Migraine in pregnancy	1 457	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	1 858	11.6	1.00 (Reference)	1.00 (Reference)
Internalizing problems				
Triptans in pregnancy	343	12.2	1.07 (0.78, 1.47)	0.97 (0.68, 1.37)
Migraine in pregnancy	1 482	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	1 884	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	1 479	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	1 885	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.

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:				
<u>Emotionality</u>				
Triptans in pregnancy	345	49.7 (9.9)	-0.81 (-1.98, 0.37)	-1.02 (-2.33, 0.29)
Migraine in pregnancy	1 483	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	1 884	50.5 (10.2)	0.00 (Reference)	0.00 (Reference)
<u>Activity</u>				
Triptans in pregnancy	351	49.3 (10.2)	-0.80 (-1.99, 0.38)	-0.06 (-1.35, 1.23)
Migraine in pregnancy	1 493	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	1 900	50.0 (10.0)	0.00 (Reference)	0.00 (Reference)
<u>Shyness</u>				
Triptans in pregnancy	348	50.1 (10.0)	-0.39 (-1.57, 0.79)	-0.71 (-2.08, 0.65)
Migraine in pregnancy	1 480	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	1 888	49.9 (10.0)	0.00 (Reference)	0.00 (Reference)
<u>Sociability</u>				
Triptans in pregnancy	349	51.0 (10.4)	1.34 (0.12, 2.56)	1.66 (0.30, 3.02)
Migraine in pregnancy	1 492	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	1 902	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.