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Causal Inference Methods for Assessing Neurodevelopment in Children Following Prenatal Exposure to Triptan Medications: A Dissertation

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CAUSAL INFERENCE METHODS FOR ASSESSING NEURODEVELOPMENT IN CHILDREN FOLLOWING PRENATAL EXPOSURE TO TRIPTAN MEDICATIONS

A Dissertation Presented
By
Mollie Elizabeth Wood

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CLINICAL AND POPULATION HEALTH RESEARCH

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Dedication

For my parents, who never doubted me for an instant- or if they did, never let on.
It's amazing what unwavering support can do for a kid.

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ABSTRACT

Background: Migraine headache is a chronic pain condition that affects 20% of women of reproductive age, and is often treated with triptans. Triptans are serotonin 1B, 1D, and 1F receptor agonists that act as vasoconstrictors and inhibitors of the trigeminal cervical complex as well as peripheral neurons; they cross the blood brain barrier and placenta, and as such are plausible neurodevelopmental teratogens. No studies have examined risk of neurodevelopmental problems in children with prenatal triptan exposure. This dissertation had three aims: (1) to examine risk of behavioral problems in children using in the presence of time-varying confounding by concomitant medication use; (2) to examine risk of temperamental, motor, and communication disturbances associated with prenatal triptans exposure, adjusting for unmeasured confounding by migraine type and severity; and (3) to examine changes in neurodevelopment over time associated with prenatal triptan exposure.

Methods: This dissertation used data from the Norwegian Mother and Child Cohort Study, a prospective birth cohort including more than 100,000 women recruited during their first prenatal ultrasound visit. Aims 1 and 3 used marginal structural models to assess the risk of (1) neurodevelopmental problems at age 36 months (Aim 1), or (2) change in risk of neurodevelopmental problems from 18 to 36 months (Aim 3) associated with prenatal triptan exposure. Aim 2 used propensity matching and calibration to adjust for unmeasured confounding by migraine type, severity, and attitudes towards medication use in pregnancy. Neurodevelopmental outcome measures included the Child Behavior Checklist (CBCL), the Emotionality, Activity, and Temperament Scale (EAS), and the Ages and Stages Questionnaire (ASQ). Exposure to triptans was ascertained by self-report.

Results: Prenatal triptan exposure was associated with greater externalizing behavior problems at 18 and 36 months, as well as greater increases in emotionality and activity from 18 to 36 months. We observed no association between triptan exposure and motor skills or communication problems; triptan use during pregnancy was associated with migraine severity but not migraine type, and adjustment for unmeasured migraine characteristics moved effect estimates towards the null.

Conclusions: Prenatal triptan exposure is associated with externalizing-type behaviors and temperament in children, while migraine itself is associated with internalizing-type behaviors and temperament. The use of concomitant medications and the severity of the underlying condition both exerted substantial influence on observed effect estimates, and should be considered in any future studies of triptan medication use in pregnancy.

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Abbreviations

Abbreviation	Definition
5-HT	Serotonin
ACE	Angiotensin converting enzymes
ADHD	Attention-deficit/hyperactivity disorder
ARBs	Angiotensin II receptor blockers
ASQ	Ages and Stages Questionnaire
ATC	World Health Organization Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
BMQ	Beliefs About Medications Questionnaire
CBCL	Child Behavior Checklist
CI	Confidence interval
EAS	Emotionality Activity and Shyness Questionnaire
EFNS	European Federation of Neurological Societies
FDA	Food and Drug Administration
GEE	Generalized estimating equations
IPCW	Inverse probability of censoring weights
IPTW	Inverse probability of treatment weights
MBRN	Medical Birth Registry of Norway
MIGSEV	Migraine Severity Scale
MoBa	The Norwegian Mother and Child Cohort Study
MSM	Marginal structural model
NNH	Number needed to harm
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OTC	Over the counter (specifically for medications)
PPV	Positive predictive value
PS	Propensity score
RD	Risk Different
RR	Risk Ratio
r-RR	Ratio of risk ratios
SCL	Symptom Checklist
US	United States
WHO	World Health Organization

CHAPTER I

INTRODUCTION

I.1 Medication use during pregnancy

The use of prescription medications during pregnancy has increased dramatically in recent years, not only in the United States but worldwide as well. Prevalence estimates from the National Birth Defects Study and the Slone Epidemiology Center Birth Defects Study found that by 2008, approximately 70% of women in the United States (US) used at least one prescription medication during pregnancy, and that the proportion of women who took four or more medications increased 2.6-fold in 30 years.[1] Additionally, a study based in the Health Maintenance Research Network Center for Education and Research on Therapeutics found that a medication other than a vitamin or mineral supplement was prescribed in 64% of pregnancies, and that more than 40% of these prescriptions were for medications classified by the Food and Drug Administration (FDA) as belonging to category C, D, or X,[2] categories indicating possible or probable harm to exposed fetuses. Analgesic medications are the third most commonly-prescribed therapeutic class, after anti-infectives and respiratory treatments, and are used in nearly 20% of pregnancies.[2] Prevalence estimates of prescription medication use during pregnancy in countries other than the United States suggest a similar secular increase, although overall rates tend to be lower.[3] Rates of prescription medication use during pregnancy are highest during the first trimester,[2] a finding that is likely in part attributable to the fact that nearly half of all pregnancies in the United States are unplanned.[4]

Studies of the effects of prenatal exposure to prescription medications most often focus on immediate pregnancy and delivery outcomes such as miscarriage/spontaneous abortion, congenital malformations, low birth weight, pre-eclampsia, and preterm birth, while far fewer studies have examined long-term outcomes, such as neurodevelopment.

I.2 Migraine headache during pregnancy

Migraine headache is a debilitating condition that most frequently affects women: in surveys of the United States population, prevalence of migraine is approximately 18-22% in women of reproductive age.[5,6] Among migraineurs, nearly one third experience attacks severe enough to require bed rest.[5] Pregnancy alters migraine attack frequency and severity: approximately 2 in 3 women experience the same or worsened severity during pregnancy, while 1 in 3 experience improvement in their symptoms.[6,7] However, this effect attenuates in multiparous women.[6] By contrast, between 1.3% and 18% of women experience their first migraine episodes during pregnancy,[7] and higher parity is associated with increased risk of migraine over the life course.[8]

Treatment options for migraine are primarily pharmacologic, and include both preventive medications as well analgesic medications, which are taken in response to an oncoming migraine episode. Preventive medications include β-blockers, antiepileptic drugs, angiotensin II receptor blockers (ARBs), angiotensin-converting enzymes (ACE) inhibitors, and calcium channel inhibitors.

Analgesic medications used for migraine include both prescription and over-the-counter (OTC) drugs, including acetaminophen, NSAIDs, opioids, muscle relaxants, ergot alkaloids, and triptans. Among the analgesic medications, triptans, a class of serotonin 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor agonists, are the most common prescription migraine medication given for acute treatment of migraine.[9] There are seven triptans commercially available worldwide: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan.

I.3 Safety of triptans during pregnancy

Triptans are considered a Category C medication by the FDA, indicating that animal studies have demonstrated a risk to the fetus associated with exposure, but that no adequate and well-controlled trials exist in pregnant women. To date, ten studies, including a total of more than 6,000 exposed infants, have examined triptan exposure during pregnancy as a risk factor for pregnancy and very early life outcomes. Triptan exposure has been associated with increased risk of spontaneous abortion/miscarriage/fetal death,[10] congenital malformations,[12] and preterm birth/prematurity/gestational age;[11–13] however, differences in sample size comparison groups have led to conflicting reports. Two recent reviews report equivocal findings on the safety of triptans: a recent meta-analysis concluded that triptan exposure did not increase the risk for malformations or preterm birth, but that triptan-exposed pregnancy had a higher

rate of spontaneous abortion, and untreated migraine had a higher rate of congenital malformations,[14] and a recent review (without meta-analysis) has recommended that if use of acetaminophen for acute migraine attack does not provide sufficient relief, conservative use of triptans during pregnancy may be considered.[15] Both studies make note of the fact that much of the current literature on triptan safety is limited by the lack of a disease control group; that is, that several existing studies do not include a comparison group of migraineurs who did not use triptans during pregnancy.

Triptans have three main mechanisms of action: they act as vasoconstrictors in smooth muscle tissue, and particularly as cranial vasoconstrictors; they also inhibit peripheral neuronal activity, and inhibit transmission in the trigeminal cervical complex.[16] Although much attention has been focused on the role of 5-HT_{1A} receptors in the developing brain,[17] recent evidence has suggest that other receptor subtypes are also important for fetal brain programming, including the 5-HT_{1B} and 5-HT_{1D} subtypes activated by triptans.[18–20] The disruption of 5-HT_{1B}/5-HT_{1D} signalling during fetal brain development resulted in abnormal thalamocortical neurons.[18] The thalamocortical pathway has previously been identified in neuroimaging studies as a brain network associated with attention-deficit/hyperactivity disorder (ADHD).[21] In addition, triptans are small, lipophilic molecules that readily cross the placenta and the blood-brain barrier. As such, triptans are plausible neurodevelopmental teratogens; however, no prior studies have examined the

neurodevelopmental sequelae of fetal exposure to triptans. The etiology of childhood neuropsychiatric and neurodevelopmental disorders is not well understood, although children are at higher risk if born to a parent with neuropsychiatric illness.[22,23] In addition, rising rates of childhood-onset neuropsychiatric disorders, developmental delay, and related conditions put a substantial financial burden on families and the healthcare and educational systems in the US.[24,25] Understanding potential risk factors for neurodevelopmental disorders, particularly modifiable risk factors such as medication exposure during pregnancy, could provide important insights into the causes of these disorders.

I.4 Methodological challenges

Studying the safety of triptans during pregnancy requires careful consideration of several complex confounding problems. First, it is necessary to consider the role of the underlying condition, migraine, as a possible cause for any observed differences between children with prenatal triptan exposure and those unexposed. Confounding by indication is a form of bias that is notoriously difficult to adequately control.[26] Migraine itself may be an independent risk factor for neurodevelopmental problems: migraine shares genetic susceptibility with several psychiatric disorders, including depression and anxiety.[27,28] Because these disorders are themselves heritable, and often have their origins in early childhood,[29] failing to consider migraine characteristics, including type and

severity, could lead to incorrectly attributing an effect to triptans that more properly belongs to the condition for which triptans were prescribed.

Second, women who take triptans during pregnancy also take many other medications, including both antidepressants and acetaminophen, both of which have previously been associated with neurodevelopmental problems in children.[30–33] In addition, triptans are taken episodically, in response to impending migraine onset: a women with migraine may take a triptan once, many times, or not at all over the course of her pregnancy. Similarly, use of other analgesic medications will also vary over time: these other medications are simultaneously confounders (common cause exposure and outcome) and mediators (on the causal pathway between exposure and outcome). Failure to adjust for concomitant medication may result in estimates biased further from the null, while adjusting for these medications can results in unpredictable bias. As a result, the case of time-varying exposure with time-varying confounding requires special consideration.

Finally, while studying child neurodevelopment at a single time point is important, the best understanding of neurodevelopment comes from considering the trajectory over time. Brain development begins in the first trimester of fetal life, but it continues throughout childhood and into early adulthood. If differences in neurodevelopmental outcomes exist between children with and without prenatal triptan exposure, understanding differences in trajectory over time may

yield important insights into the mechanism by which triptans affect the developing brain.

I.5 Summary

Understanding the possible risks of medication exposure during pregnancy of necessity relies upon the use of observational data, as pregnant women are routinely excluded from randomized clinical trials for ethical reasons. Studies of the safety of medication use during pregnancy, therefore, must carefully balance the need for accurate risk estimates against the potential for falsely alarming women and prescribers, and thereby depriving women of needed medications. The purpose of this dissertation is to apply causal inference techniques and other methods to obtain unbiased estimates of the effect of prenatal triptan exposure on neurodevelopment in children. The findings from this work will have implications for clinicians who treat pregnant women with migraine headache.

CHAPTER II

PRENATAL TRIPTAN EXPOSURE INCREASES EXTERNALIZING BEHAVIORS AT THREE YEARS: RESULTS FROM THE NORWEGIAN MOTHER AND CHILD COHORT STUDY

Prenatal triptan exposure increases externalizing behaviors at three years: results from the Norwegian Mother and Child Cohort Study

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II.0 Abstract

Background. Triptans are serotonin agonists given for the acute treatment of migraine, a chronic pain condition that is highly prevalent in women of childbearing age. No previous studies have examined associations between prenatal triptan exposure and neurodevelopment in children.

Methods. This questionnaire-based study was set in the Norwegian Mother and Child Cohort study, a prospective birth cohort that includes nearly 40% of all pregnancies in Norway from 1999-2008. 41,173 live, singleton births without major malformations who responded to the 36-month post-partum follow-up questionnaire were included in this study, of which 396 used a triptan during pregnancy, 798 used a triptan prior to pregnancy only, 3291 reported migraine without triptan use, and 36,688 reported no history of migraine or triptan use. The Internalizing and Externalizing subscales of the Child Behavior Checklist were the main outcome measures for this study. We employed a cutoff score of T>65 to indicate symptoms that were present at clinically relevant levels.

Results. Children exposed to triptans during pregnancy had a 1.39-fold increased risk of externalizing behaviors compared to those whose mothers used triptans prior to pregnancy only (95% CI: 0.97 to 1.97), a 1.36-fold increased risk compared to the unmedicated migraine group (95% CI: 1.02 to 1.81), and a 1.41-fold increased risk compared to the population comparison group (95% CI: 1.08 to 1.85). The greatest risk was associated with first trimester exposure (RR: 1.77,

95% CI: 0.98, 3.14). Risk differences were small, ranging from 3-6%. No association was observed between triptan exposure and internalizing behaviors. Conclusions. This study found an increased risk of clinically-relevant externalizing behaviors in children with prenatal exposure to triptans, and this risk was highest for first trimester exposure. However, absolute risks were small, and the results may be due to confounding by underlying migraine severity.

II.1 Introduction

Migraine headache, characterized by debilitating pain and significant disability, affects between 18% and 22% of women and is most common in women of childbearing age.[5,6] Treatment for migraine is primarily pharmacologic including prescription medications (e.g., triptans, opioids) and over-the-counter medicines (e.g. acetaminophen and non-steroidal anti-inflammatory drugs (NSAID)). The European Federation of Neurological Societies (EFNS) recommends no triptan use during pregnancy unless the developing fetus is at great risk from the untreated maternal migraine,[34] while the Food and Drug Administration (FDA) has assigned triptans a C-category rating,[7] suggesting lack of evidence for both maternal and fetal safety. This lack of safety data leaves women and prescribers with uncertainty and may result in under-treatment of severe pain. Pregnancy outcomes following exposure to triptan medications have been studied prospectively.[12,35–37] No increased risk of congenital malformations was observed, although several studies noted an increased risk for poor pregnancy outcomes, including pre-eclampsia or hypertension, preterm birth, atonic uterus, and folate-deficient anemia.[12,37] To our knowledge, no studies have examined neurodevelopment following prenatal triptan exposure.

Neurodevelopmental outcomes, such as internalizing symptoms, characterized by inward emotional states (e.g. depression, shyness, anxiety) and externalizing symptoms (e.g. aggression) are important outcomes to study. Internalizing symptoms are predictive of future anxiety disorders[38] and panic

attacks,[39] and externalizing behaviors predict future depression and disruptive behavior.[38] Triptans are serotonin 5-HT agonists that act both as vasoconstrictors and inhibitors of the trigeminocervical complex,[40] and are thought to cross the blood-brain barrier.[41] Serotonin is involved in all stages of neurodevelopment.[17] Other pharmacologic agents that effect serotonin homeostasis, such as selective serotonin reuptake inhibitors, have been associated with an increased risk for autism spectrum disorders[42,43] and attention-deficit/hyperactivity disorder[44,45] in children.

Understanding potential risk factors for neurodevelopmental disorders could provide important insights into the causes of these disorders. This study is set in the Norwegian Mother and Child Cohort Study, a prospective birth cohort with information on prescription and over-the-counter medication use over time during pregnancy. The aim of this study was to investigate the possible association of prenatal triptan exposure and behavioral problems in three-year-old children, using causal inference methods.

II.2 Methods

Study Sample

The Norwegian Mother and Child Cohort Study (MoBa) was established by the Norwegian Institute of Public Health and recruited participants from 1999-2008. Women were invited to participate prior to routine ultrasound appointments (pregnancy weeks 13-17). A total of 108,841 women consented;

these women comprise 38.7% of the pregnancies in Norway during the study period. Participation rates for the six month post-partum and 36 months post-partum questionnaires were 84.8% and 60.2%, respectively.[46] The MoBa study, including participation and retention rates, has been described in greater detail elsewhere.[47] Written informed consent was obtained from all participants, and the study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate; this analysis was granted an exemption from the University of Massachusetts Medical School Institutional Review Board. Data were taken from the quality-ensured Data Version 6, released by MoBa in 2012 and includes all children born before 2009 for whom the age 3 years questionnaire was received by May 4, 2011; these data were linked to the Medical Birth Registry of Norway (MBRN) using participants' 11-digit personal identification numbers.

Because this study focused on infant neurodevelopment, we excluded infants not born alive (N=680), multiplet births (N=3,801), and infants born with major congenital malformations or chromosomal abnormalities (N=3,204); further, we excluded women who reported triptan exposure but did not report whether exposure occurred prior to or during pregnancy (N=14); in total, 7,220 pregnancies were excluded, leaving an initial study sample of 101,644 women. Comparisons of included and excluded pregnancies revealed that excluded women were older, had higher body mass indices (BMI), were more likely to be primiparous, and were more likely to have reported using antidepressants or

benzodiazepines during pregnancy. At the 36-month follow-up, 41,173 participants had complete data on the main outcome measure. The flow through the study is outlined in Figure 2.1.

Ascertainment of triptan exposure

Information on exposure to medications was gathered prospectively from two prenatal (Q1, Q3) and one postpartum questionnaire (Q4). Women were asked to indicate when they had taken a medication (during the six months before pregnancy, during weeks 0-4, 5-8, 9-12, and/or 13 or later for Q1, during weeks 13-16, 17-20, 21-24, 25-28, and/or week 29 or later for Q3, and from week 30 until birth for Q4), and to write the name of the medication in a text box. Women who indicated multiple medications in a single text box (e.g., sumitriptan and acetaminophen) were assumed to have been exposed to all listed medications in all time periods. Medications were classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System.[48] The ATC code N02CC was used to determine triptan exposure. Triptan medications were further classified into specific compounds: N02CC01 (sumatriptan), N02CC02 (naratriptan), N02CC03 (zolmitriptan), N02CC04 (rizatriptan), N02CC05 (almotriptan), N02CC06 (eletriptan), and N02CC07 (frovatriptan). No information was available on formulation (tablet vs. injection or nasal spray) or dose. Because triptan exposure is relatively rare, timing of exposure was collapsed into trimester categories (pre-pregnancy, first trimester, second/third trimester, use during pregnancy with unknown timing). No

data are available on sensitivity and specificity of triptan medication recall during pregnancy; estimates of accuracy of maternal recall of psychotropic medication give positive predictive values (PPV) of 85.9%,[49] sensitivity of 0.21 – 0.57, and specificity of 0.99 — 1.00, while recall of analgesic medication use in pregnancy may vary between 0.17 -- 0.41 (sensitivity) and 0.96 -- 0.99 (specificity), respectively.[50] These values suggest that women may forget medication use, but that any reported use is unlikely to be a false positive.

Ascertainment of outcome

Internalizing and externalizing behaviors tend to be relatively stable over multiple measurements,[29] including measurements conducted in early childhood predicting problems in adolescence.[51] Thus, the Child Behavior Checklist (CBCL), a validated measure of child behavior widely used in both clinical and research practice, was used to define neurodevelopmental outcomes at age 3 years. A shortened version was used in MoBa; this version has been validated in a Norwegian population.[52] The externalizing (including the "attention problems" and aggressive behavior" subscales) and internalizing (including the "emotionally reactive," "anxious/depressed," and "somatic complaints" subscales) domains were used. Standardized z-scores were computed for the study sample; scores were further classified as being clinically meaningful ($z \geq 1.50$, equivalent to a T score of 65).

Potential confounders and mediators

Confounders were identified through literature review and selected through iterative use of directed acyclic graphs (dagitty.net). Maternal age, pre-pregnancy BMI (underweight or <18.5 kg/m^2, normal weight or 18.5-25 kg/m^2, or overweight, >25 kg/m^2 according to WHO guidelines), education (primary or secondary vs university or higher), marital status (married or cohabiting vs other), parity (multiparous vs. primiparous) were all ascertained by self-report on Q1. Smoking (ever during pregnancy vs. not during pregnancy) and alcohol use (ever during pregnancy vs. not during pregnancy) were ascertained by combining information from self-report as well as linkage to the Medical Birth Registry of Norway (MBRN). Maternal symptoms of depression and anxiety, were assessed using the Symptom Checklist 8 (SCL-8), a short version of the SCL-25.[53] The SCL-8 is highly correlated with the SCL-25 and has been widely used in surveys of mental health. The SCL-8 is administered via self-report at Q1 and Q3. Standardized z-scores were computed at each time point, and an average SCL-8 score was used in the models.

Confounding by indication, in which the condition underlying medication use is the true cause of the outcome, rather than the medication use itself, is important to address when studying medication exposure during pregnancy. Because migraine and depression have significant shared genetic susceptibility,[54] and because migraineurs who take triptans also use many other medications, some of which have been associated with neurodevelopmental problems in children,[30,31] obtaining unbiased estimates of the effect of prenatal

triptan exposure on neurodevelopment requires careful consideration of underlying disease severity as well as concomitant medication use. Women were specifically asked about history of migraine at Q1 only, and were classified as having migraine headache if they indicated had migraines or had taken migraine medications. Migraine headache may be treated with medications other than triptans, including analgesics such as aspirin, non-steroidal anti-inflammatory drugs (NSAID), acetaminophen, and opioids.[7] Other medications considered as potential confounders were psychotropic medications, including antidepressants, benzodiazepines, and anti-seizure medications. The following ATC codes were used: N02BE01 (acetaminophen), N02A (opioids), M01A (non-steroidal anti-inflammatory drugs, NSAIDs), N06A (antidepressants), N05CD02, N05CD03, N05CD08, N05BA01, N05BA05, N05BA12 (benzodiazepines), and N03A (anti-convulsants). All co-medications were categorized both as ever vs. never used in pregnancy and according to timing (pre-pregnancy, first trimester, second/third trimester). Because previous research has indicated an effect of acetaminophen dose on child neurodevelopment,[30] we also considered acetaminophen exposure as a three-category variable: no trimesters exposed, one trimester exposed, or two or more trimesters exposed.

Potential mediators —that is, factors that could be caused by triptan exposure and also effect later neurodevelopment—included several intermediate pregnancy outcomes: small for gestational age (defined as below the 10th percentile for gestational age[55]), preterm birth (born before gestational week 37),

and five minute Apgar score (7 or higher vs <7). Mediators were identified through linkage to the Norwegian Medical Birth Registry (MBRN).

Missing data for important confounders were assessed, and rate of missingness was low (<5% missing) as well as nondifferential with respect to exposure group. We elected to conduct a complete case analysis, excluding 6,856 women who were missing data on at least one confounder (Figure I.1). We conducted sensitivity analyses to better understand the possible impact of two potential sources of bias: residual confounding by acetaminophen exposure, and unmeasured confounding by migraine severity. To address the former concern, we repeated our main analyses in a subgroup of women who did not report acetaminophen exposure during pregnancy (n=22581). To address confounding by migraine severity, which was not measured in MoBa, two approaches were taken. First, we compared the risk of behavior problems between different disease exposure groups: a group of women who discontinued triptan use prior to pregnancy, a group with migraine headache but no history of triptan use, and a population comparison group with no migraine or triptan history. These disease comparison groups may be thought of as a proxy for migraine severity, and as such, we expected to see a dose-response relationship between comparison group and behavioral symptoms, in which the highest risk of behavior problems is present in the women who used triptans in pregnancy, and progressively lower risks present in triptan discontinuers and women with migraine but no triptan history; further, because migraine is associated with an

internalizing disorder, depression, we would expect to see a stronger association with internalizing rather than externalizing behavior. Second, we used probabilistic bias analysis to quantify the possible bias introduced by migraine severity, using Excel spreadsheets developed by Lash, Fox, and Fink.[56] We used prevalence estimates for severe migraine ranging from 0.20 to 0.40, which are consistent with recent population estimates,[57] and assumed that severe migraine was twice as prevalent in triptan users as in women who discontinued triptan use prior to pregnancy. We allowed the association between the unmeasured confounder, migraine severity, to vary between 1.25 and 4.00, and conducted 10,000 simulations for each combination of bias parameters.

Statistical methods

Our analysis proceeded in several steps. First, we estimated the prevalence of triptan use overall and by trimester. We then evaluated descriptive statistics by triptan use to better understand the population and factors that may confound the triptan-neurodevelopmental relationship. Because co-medication use was likely, we examined prevalence of comedication in triptan users and non-users throughout pregnancy. Two modeling approaches were applied: Poisson models and marginal structural models.

Poisson Models

Modified Poisson models were used to obtain risk ratios and risk differences for the association between triptan exposure and clinically significant behavioral problems; 95% confidence intervals were calculated using robust

standard errors.[58] Models were adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, co-medication use (NSAIDs, acetaminophen, opioids, and antidepressants), depression/anxiety symptoms, smoking, and alcohol use. Considered individually, none of the confounders changed the estimate of effect by more than 10%. To better understand the effects of timing of triptan exposure, we examined the risk of triptan exposure for prenatal, first trimester, and second/third trimester exposure within a subsample of women who reported a history of migraine headache.

As part of the sensitivity analyses described above, we compared the risk of behavioral problems in children prenatally exposed to triptans to three reference groups. To partially address issues of confounding by migraine severity, we identified a group of children whose mothers used triptans in the six months prior to pregnancy but discontinued use in pregnancy; we also compared prenatally exposed children to children whose mothers reported a history of migraine, but did not report any use of triptans during pregnancy or in the six months priors, and finally, to a population comparison group whose mothers reported no history of migraine or triptan use.

Marginal Structural Models

The second modeling approach used was a marginal structural model analysis. This allowed us to account for possible effects of time-varying exposure and confounding and to determine the extent to which any observed effects of triptan exposure might be mediated through intermediate birth outcomes. Triptan

medications are taken in response to an oncoming migraine attack, and as such their use will change over time during pregnancy: a migraineur may take a triptan only prior to pregnancy, during the first trimester, during later trimesters, or at multiple times. In addition, her use of triptans may be confounded by other factors, such as concomitant medication use, which may also change over time. For example, first trimester triptan exposure might be associated with second trimester acetaminophen use, which in turn could be associated with third trimester triptan use (Figure 2.2). In this case, acetaminophen is both a confounder and a mediator: if acetaminophen is associated with increased risk of behavioral problems, then failing to adjust for acetaminophen use will cause an overestimate of the effects of triptan exposure, but adjusting for acetaminophen use will result in a bias of the effect estimate towards the null. To consider the possible scenario in which time-varying confounders are also mediators, we performed a marginal structural model analysis using methods described by Robins & Hernan[59,60] as well as Bodnar.[61] We constructed stabilized inverse probability of treatment weights ($IPTW_s$) via logistic regression,[62] in which exposure at each time point (pre-pregnancy, first trimester, second/third trimester) was the dependent variable and predictors in the model included baseline confounders (maternal age, pre-pregnancy BMI, education, marital status), time-invariant confounders (smoking and alcohol use during pregnancy, severity of depressive symptoms in pregnancy) and triptan history.

The stabilized IPTW for each individual *i* at each measurement occasion *t* is:

$$sw_i^t(t) = \prod \frac{Pr[TRP_{it}=trp_{it} \mid \overline{TRP}_{it}=\overline{trp}_{it}, CON=con_{it}]}{Pr[TRP_{it}=trp_{it} \mid \overline{TVC}_{i(t-1)}=\overline{tvc}_{i(t-1)}, CON=con_{it}]}$$

where *TRP*, *CON*, and *TVC* are random variables representing triptan exposure, baseline confounders, and time-varying confounders, respectively, and *trp*, *con*, and *tvc* are the observed values for these random variables for each individual *i.* Overbars indicate the history of each variable up to the measurement occasion *t.* We ruled out the need to truncate the weights at the 99th and 95th percentiles as doing so did not substantially alter the results. The MSM approach has the effect of achieving balance of confounders within strata of exposure; if the confounders are also mediators (see Figure 2.2 for illustration), this approach may reduce bias induced by inappropriate control for an effect on the causal pathway. The MSM approach produces unbiased effect estimates if the assumptions of consistency, exchangeability and positivity are met, although the reduction in bias also comes with an increase in variance.[62] While not formally testable, we took steps to evaluate whether the assumptions of exchangeability and positivity were met. To strengthen the assumption of positivity, which requires that all individuals in the sample have a non-zero probability of exposure, we limited MSM analyses to women with a reported history of migraine, reasoning that triptan medications are only prescribed for migraine headache, and inclusion of non-migraineurs could result in structural zeroes. Unmeasured confounding by migraine severity may pose a threat to exchangeability; to examine this, we compared concomitant medication use rates of women who took triptans during pregnancy compared to

women who discontinued use of triptans, or those who had no history of triptan use. After constructing stabilized weights, we fit a weighted Poisson model with robust standard errors to account for clustering induced by weighting.

We used a SAS macro developed by Vanderweele and Valeri[63] to quantify the direct effects of prenatal triptan exposure on neurodevelopment, as well as the indirect effects of triptan exposure mediated through birth outcomes, including birth weight, gestational age, and 5 minute Apgar score; because our analyses did not reveal significant indirect effects of triptan exposure through individual mediators, we have not included the results of the mediation analyses in this report. All analyses were carried out using SAS version 9.3.

II.3 Results

Prevalence of triptan use during pregnancy was 1.1%, and prevalence of use prior to pregnancy was 3.0%. 10.9% of women reported a history of migraine prior to pregnancy or up to the 13th week of pregnancy (pregnancy questionnaire 1). Among those women who reported triptan use, 94.6% used triptans prior to pregnancy, 25.6% used triptans in the first trimester, and 10.6% reported use in the second or third trimesters. Based on self report of medication use and migraine history, women were further classified into four exposure groups: triptan exposure during pregnancy (N=396), six months prior to pregnancy but not during pregnancy (N=798), history of migraine without triptan use (N=3,291), and a population comparison group in which no history of migraine or triptan use was

reported (N=36,688). The characteristics of the study sample for these groups are outlined in Table 2.1. Among women with a history of triptan use, women who used triptans during pregnancy were slightly older and were more likely to be multiparous. In addition, they had higher rates of pre-pregnancy opioids, antidepressant, and benzodiazepine use, and were more likely to use opioids, acetaminophen, NSAIDs, antidepressants, and benzodiazepines during pregnancy, compared to women who discontinued triptan use during pregnancy. Descriptive analysis suggested that the four exposure groups we identified had distinct medication use patterns over time (Figure 2.4). Women with a history of triptan use also had higher rates of preventive therapy than women with migraine but no triptan history. Women who took triptans during pregnancy also had higher rates of pre-eclampsia. Infants prenatally exposed to triptans were more likely to be born preterm and to have a five-minute Apgar score below seven.

Sumitriptan was by far the most commonly used medication, followed by zolmitriptan and rizatriptan (Table 2.2). The rank order of medication did not vary by time of use during pregnancy.

Externalizing behaviors

Externalizing symptoms at or above a clinical cutoff of T>65 were present in 11.6% of children exposed to triptans *in utero*, compared to 8.3% in children whose mothers use triptans prior to pregnancy only, 9.1% in children whose mothers reported migraine with no triptan use, and 7.7% in a population comparison group (Figure 2.3A). Table 2.3 shows that children whose mothers

used triptans during pregnancy had a 36% increased risk of clinically-relevant externalizing behaviors compared to a population comparison group (RR_{adj}: 1.36, 95% CI: 1.04 to 1.79). We observed similar risks when comparing children with prenatal triptan exposure to children whose mothers reported migraines but no triptan use (RR_{adj}: 1.33, 95% CI: 1.00 to 1.78) as well as to children whose mothers used triptans prior to pregnancy only (RR_{adj}: 1.36, 95% CI: 0.96 to 1.94). The risk of externalizing behavioral problems was highest children exposed to triptans in the first trimester (13.2%) and lowest in women reporting use in 2nd and 3rd trimester (8.0%) (Figure 2.3B). When we examined risks of externalizing behavior associated with windows of exposure to triptans among women with a history of migraine (N=4,439), first trimester exposure was associated with a 77% increased risk in multivariable-adjusted Poisson models (95% CI: 1.23 to 3.56), while no increased risk was observed for pre-pregnancy exposure. Estimates of effect from marginal structural models were similar, although 95% confidence intervals were considerably wider: first trimester exposure was associated with a 75% increased risk of externalizing symptoms in the clinical range (RR_{MSM}: 1.75, 95% CI: 0.98 to 3.14), while pre-pregnancy (RR_{MSM}: 0.99, 95% CI: 0.77 to 1.27) and second/third trimester (RR_{MSM}: 0.59, 95% CI: 0.23 to 1.51) exposure showed no evidence of increased risk.

The absolute risk for first trimester triptan exposure was 6% (95% CI: -0.02 to 0.15), which is equivalent to a number needed to harm (NNH) of 17.

Internalizing behaviors

Fewer children in our sample exhibited clinically meaningful internalizing symptoms than externalizing symptoms (Figures II.3A and B). Comparing children born to women who used triptans during pregnancy to those whose mothers used triptans prior to pregnancy only (RR_{adj}: 0.78, 95% CI: 0.51 to 1.21), those with migraine but no triptan use (RR_{adj}: 0.89, 95% CI: 0.61 to 1.30), and a population comparison group (RR_{adj}: 1.02, 95% CI: 0.71 to 1.47) revealed no increased risks of internalizing behavior problems in the clinical range; absolute risks were zero or near zero for all comparisons (Table 2.4). An analysis of women who did not use acetaminophen during pregnancy revealed similar point estimates to the main set of analyses; however, the smaller sample size, which included only nine triptan-exposed children with externalizing behavior problems and six with internalizing problems, resulted in wider confidence intervals that included the null (results not shown). Estimates of the effect of triptan exposure at specific times revealed inconsistencies between multivariable adjusted Poisson models and marginal structural models (Table 2.S1). Multivariable models showed an increased risk of internalizing symptoms associated with pre-pregnancy (RR_{adj}: 1.27, 95% CI: 1.01 to 1.59) but not during pregnancy; MSM estimates showed no association between pre-pregnancy exposure and internalizing behaviors (RR_{MSM}: 1.04, 95% CI: 0.80 to 1.35). Absolute risks were near zero, with 95% confidence intervals that included the null.

Sensitivity Analyses

Contrasts between the disease comparison groups (i.e., comparing the pre-pregnancy use only group to the population comparison group) revealed risk ratios near 1.0 and risk differences near 0.0, indicating no increased risk of externalizing symptoms for women with migraine who avoided triptan use or discontinued use prior to pregnancy (Table 2.S2). We observed a 31% increased risk of internalizing symptoms in women who discontinued triptans prior to pregnancy compared to the population comparison group (95% CI: 1.04 to 1.65), and a 14% increased risk for the unmedicated migraine group versus the population comparison group (95% CI: 1.01 to 1.30), suggesting that the underlying illness may increase the risk for internalizing symptoms.

Probabilistic bias analysis showed that, using bias parameters that we considered reasonable based on existing literature (an association between migraine severity and externalizing symptoms of RR=1.50, prevalence of severe migraine of 40% in triptan users and 20% in triptan discontinuers), the association between triptan use and externalizing symptoms were slightly reduced (RR: 1.40 vs. bias-corrected RR: 1.29). To completely explain the increased risk associated with triptan use, an association between migraine severity and externalizing behavior would have had to have been at least 4.0 (Table 2.S3).

II.4 Discussion

In this prospective study of prenatal exposure to triptan medication and risk of neurodevelopmental problems in three-year-old children, we observed a consistent, near-40% increased risk of externalizing behavior problems in the clinical range among children born to mothers who used triptans during pregnancy, compared to those who used triptans prior to pregnancy only, those with migraine but no triptan use, and a population comparison group. This risk seems to be associated primarily with a 75% increased risk for first trimester exposure. To place our findings in a clinical context, the risks observed were modest, and the absolute risks were small. No increased risk of internalizing symptoms was noted, and exposure in pregnancy after the first trimester was not associated with an increased risk of either externalizing or internalizing symptoms.

The increasing prevalence of neurodevelopmental and psychiatric disorders in children[64,65] poses a serious public health challenge. Identifying antecedents of these disorders is vital both for understanding the pathophysiologic basis of disease, as well as providing opportunities for intervention. Externalizing disorders in very young children have been shown to have high diagnostic stability into school age,[29,66] and are predictive of major mental illness later in life, including major depression. Risk factors for externalizing symptoms, therefore, can give important insights into the origins of diseases that result in substantial impairment throughout the life course.

In studies of the risks of prenatal exposure to medication, it is particularly important to consider the possible influence of confounding by indication, especially when the indication for which the medication was prescribed is heritable[67] and suspected to have direct effects on fetal development,[68] as is the case with migraine. It is likely that women who continue to take a medication during pregnancy have a more severe course of migraine than those who discontinue its use before or early in pregnancy. In the absence of information on migraine severity, which was unavailable in the MoBa study, we have identified multiple comparison groups: a group of women who discontinued triptan use prior to pregnancy, a group with migraine headache but no history of triptan use, and a population comparison group with no migraine or triptan history. These disease comparison groups may be thought of as a proxy for migraine severity, and as such, we would expect to see a dose-response relationship between comparison group and behavioral symptoms, in which the highest risk of behavior problems is present in the women who used migraines in pregnancy, and progressively lower risks are present in triptan discontinuers and women with migraine but no triptan history. Such a relationship is present for internalizing symptoms, which might be expected, given previously-described genetic links between migraine and depression.[69] However, no such relationship was observed for externalizing symptoms; rather, we noted a modest but consistent elevated risk for prenatal triptan exposure compared to all other comparison groups, and no elevated risk for externalizing behaviors in the migraine groups

that did not report triptan use. In addition, the results of probabilistic bias analysis to determine the possible effect of unmeasured confounding by migraine severity suggest that there would need to be a substantial association between migraine severity and externalizing behaviors (RR>4.0) to fully explain the observed association between triptan exposure and externalizing symptoms.

This study is the first to examine risks of neurodevelopmental problems associated with prenatal triptan exposure, and has several important strengths. First, this study compares triptan exposure during pregnancy to multiple comparison groups, including two disease comparison groups, and found a moderate but consistent elevated risk for the triptan-exposed group. Second, the study is based in a large, prospective birth cohort in which extensive medication data were available, including information on use of over-the-counter medications such as acetaminophen. Several recent studies have noted increased risks of externalizing and/or ADHD-like symptoms in children prenatally exposed to acetaminophen[30,31] as well as antidepressants,[33] making it particularly important to appropriately adjust for these potential confounders. Additionally, this study uses advanced causal inference methodology to assess the risks associated with prenatal exposure to medications. While marginal structural models are becoming more common in the epidemiologic literature, they have rarely been used to evaluate risks of pregnancy medication use. In the case of neurodevelopmental effects of medication exposure, when there is no known safe period for exposure, it is important to carefully model both time varying

exposure and confounding; failing to do so may result in biased effect estimates. In our analyses, the traditional multivariable-adjusted modeling approach indicated an increased risk of internalizing symptoms associated with pre-pregnancy triptan exposure, which was attenuated when proper adjustment was applied using marginal structural models, although it is important to note that the confidence intervals from the traditional regression-adjusted and MSM results overlapped. These innovations are particularly important in light of the high rates of concomitant medication use observed among women who took a triptan during pregnancy.

Our study has several notable limitations, which should be taken into account when considering the results. Although nearly one in four women with migraine reported using triptans either prior to or during pregnancy, the overall risk of migraine in our sample was lower than expected (10%, versus population estimates of 18-22%[5,6]). While the MoBa sample includes nearly 40% of births in Norway during the study period, previous reports have noted that participants in MoBa are healthier than the general population.[47] Women with more severe migraine and higher rates of triptan use may not have participated in this study, limiting its generalizability; however, this selection bias is unlikely to have produced inflated estimates of effect.[70]

Although we have applied several sensitivity analyses to assess the potential for confounding by indication, we cannot rule out the possibility that our findings may be explained by migraine severity or frequency. Migraine headache

is heritable,[27,54,69] and is linked to internalizing symptoms in both children and adults.[68,69] One recent study noted that children with migraine have more severe internalizing problems than children without migraine, but that this difference was attenuated after adjusting for maternal headache frequency;[68] another study noted that internalizing symptoms may indicate a prodromal migraine state.[71] No such effects have been reported for externalizing symptoms. The fact that our analysis showed an increased risk of externalizing symptoms should alleviate some concern that our findings may be explained by confounding by indication. It is also possible that the observed increased risk for externalizing problems after triptan use during pregnancy could be due to personality differences between women using medication during pregnancy and women abstaining from medication during pregnancy. Ystrom et al.[72] found that women using acetaminophen during pregnancy had lower scores on the personality trait of conscientiousness.[72] Low conscientiousness is heritable,[73] and is a core feature of externalizing problems in adults.[74] Since externalizing problems are heritable already during preschool age,[75] the association found between triptan use during pregnancy and child externalizing problems could be due to a genetic transmission of risk. An additional limitation is that despite the large sample size, the low prevalence of triptan use limited our ability to examine effects of specific triptans, as well as producing imprecise estimates of effect. While it is reassuring that few women require triptan therapy during pregnancy, replication of these findings in populations with higher rates of medication use is necessary to

determine whether specific triptans may pose greater risks to fetal development. Finally, although several triptans are available in different formulations (e.g., tablet vs. nasal spray), no information was available on dose or formulation, which precluded more subtle investigations into effects of dose on outcome. Our results should be interpreted cautiously, with these strengths and limitations in mind.

Conclusion

Prenatal exposure to triptan medications was associated with a modestly increased risk of externalizing behaviors, with the most pronounced risk associated with exposure in the first trimester. Because we are unable to rule out confounding by indication as an explanation for the observed effects, changes to prescribing practices are unwarranted at this time: caution is already recommended in the use of triptan in pregnant women, and the evidence of possible harm is not sufficient to deprive women of appropriate pharmacotherapy during pregnancy. Future studies should include information on migraine type and severity as well as medication use to ensure safe and efficacious treatment of migraine during pregnancy.

Table 2.1. Maternal characteristics, medication use, and intermediate birth outcomes of 41,173 included pregnancies

	History of triptan use		No triptan history	
	During pregnancy N=396	Pre-pregnancy Only N=798	Migraine N=3,291	No Migraine N=36,688
Age in years (Mean, SD)	30.8(4.4)	30.5(4.5)	30.3(4.5)	30.4(4.4)
BMI (kg/m^2)				
<18.5	2.8[1]	2.4	3.7	2.6
18.5-25	59.6	59.9	61.8	66.9
>25	37.6	37.2	34.5	30.5
Multiparous	49.2	45.9	53.5	53.4
Married or cohabitating	95.5	98.0	97.0	97.6
Mother Education				
Primary or secondary	31.1	31.8	37.0	31.0
University or higher	68.9	68.2	63.0	69.0
Smoking during pregnancy	11.4	11.7	13.1	11.1
Alcohol during pregnancy	20.5	15.0	15.0	17.1
Folate Supplementation	60.9	62.2	57.8	59.2
Multivitamin Supplementation	37.9	43.7	38.9	37.0
Migraine Preventive Therapy	1.8	1.8	0.6	0.0
Opioids				
Pre-pregnancy	8.1	5.3	5.1	1.3
In pregnancy	12.9	4.6	4.9	1.4
Acetaminophen				
Pre-pregnancy	46.5	47.9	44.8	25.4
In pregnancy	76.8	70.1	63.7	42.6
NSAIDs				
Pre-pregnancy	22.0	25.9	23.3	9.9
In pregnancy	22.5	11.2	12.6	5.9
Anti-convulsants				
Pre-pregnancy	0.5	0.5	0.2	0.1
In pregnancy	0.3	0.3	0.3	0.2
Antidepressants				
Pre-pregnancy	5.3	4.6	3.8	2.2
In pregnancy	2.0	1.1	1.6	0.9
Benzodiazepines				
Pre-pregnancy	1.8	1.4	0.9	0.5
In pregnancy	1.8	0.5	0.5	0.4
Maternal depressive/anxiety symptoms[1] (Mean, SD)	0.2(1.7)	0.0(1.8)	0.2(1.9)	-0.2(1.6)
Pre-eclampsia	7.8	4.3	4.0	3.5
Small for Gestational Age	6.6	6.3	6.5	6.2
Apgar 5 (<7)	1.5	1.0	0.7	0.9
Preterm	4.0	4.6	4.8	4.6
Low Birth Weight	2.0	2.3	2.6	2.4

1. Figures shown are percent of column total with the exception of maternal age and depressive/anxiety symptom severity, presented as mean(standard deviation)

Table 2.2. Specific triptan medications used before and during pregnancy

	Pre-pregnancy	First Trimester	Second/third Trimester	Pregnancy Use (TU)[2]
	N=1,131	N=304	N=137	N=46
Sumitriptan	44.3[1]	47.2	50.4	47.8
Rizatriptan	25.8	23.4	27.8	23.9
Zolmitriptan	17.3	16.8	13.9	26.1
Eletriptan	11.8	11.2	6.6	4.3
Naratriptan	2.5	3.3	5.8	2.2
Almotriptan	2.6	2.6	1.5	6.5

1.Column percentages sum to greater than 100% due to use of multiple triptans during the study period. Number of triptan users diverge from those shown on Table 1: of 1131 pre-pregnancy users, 798 used only prior to pregnancy and 333 used both before and during pregnancy.
2. "Pregnancy Use TU" refers to women who used a triptan in pregnancy but did not provide enough information to determine timing; these women were included in the main group analyses and excluded from timing models.

Table 2.3. Comparison of risk of clinically-significant externalizing behavior problems for exposure to triptans

Among all mothers (n=41,173)

	Total N	N with outcome	Crude Risk Ratio (95% Confidence Interval)	Adjusted Risk Ratio[1] (95% Confidence Interval)	Crude Risk Difference (95% Confidence Interval)	Adjusted Risk Difference[1] (95% Confidence Interval)
Triptans in pregnancy	396	46	1.40 (0.98 to 2.00)	1.36 (0.96 to 1.94)	0.03 (0.00 to 0.07)	0.02 (-0.01 to 0.06)
Vs.Triptans pre-pregnancy only	798	66	Referent	Referent	Referent	Referent
Triptans in pregnancy	396	46	1.32 (0.98 to 1.77)	1.33 (1.00 to 1.78)	0.03 (0.00 to 0.06)	0.02 (-0.01 to 0.05)
Vs. Migraine with no triptan use	3,291	289	Referent	Referent	Referent	Referent
Triptans in pregnancy	396	46	1.50 (1.14 to 1.98)	1.36 (1.04 to 1.79)	0.04 (0.01 to 0.07)	0.02 (-0.01 to 0.05)
Vs. Population (no triptan use or migraine)	36,688	2,828	Referent	Referent	Referent	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSAIDs, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.
2. Marginal structural models weighted with stabilized inverse probability of treatment weights, constructed at each time point using baseline confounders, time-invariant confounders, and medication history.

Table 2.3 (Continued)

Among mothers with migraine (n=4,439)						
	Total N	N with outcome	Crude Risk Ratio (95% Confidence Interval)	Marginal Structural Model Risk Ratio[2] (95% Confidence Interval)	Crude Risk Difference (95% Confidence Interval)	Marginal Structural Model Risk Difference[2] (95% Confidence Interval)
Pre- pregnancy triptan use	1,085	101	0.94 (0.73 to 1.20)	0.99 (0.77 to 1.27)	-0.02 (-0.05 to 0.01)	-0.02 (-0.05 to 0.00)
Vs. No pre-pregnancy use	3,354	297	Referent	Referent	Referent	Referent
Triptans in 1st trimester	304	40	1.77 (1.23 to 2.56)	1.75 (0.98 to 3.14)	0.06 (0.01 to 0.10)	0.06 (-0.02 to 0.15)
Vs. No triptan use in 1st trimester	4,135	358	Referent	Referent	Referent	Referent
Triptans in 2nd /3rd trimester	137	11	0.64 (0.34 to 1.19)	0.59 (0.23 to 1.51)	-0.02 (-0.07 to 0.02)	-0.02 (-0.11 to 0.07)
Vs. No triptan use in 2nd/3rd trimester	4,302	387	Referent	Referent	Referent	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSAIDs, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.
2. Marginal structural models weighted with stabilized inverse probability of treatment weights, constructed at each time point using baseline confounders, time-invariant confounders, and medication history.

Table 2.4. Comparison of risk of clinically-significant internalizing behavior problems for exposure to triptans

Among all mothers (n=41,173)

	Total N	N with outcome	Crude Risk Ratio (95% Confidence Interval)	Adjusted Risk Ratio[1] (95% Confidence Interval)	Crude Risk Difference (95% Confidence Interval)	Adjusted Risk Difference[1] (95% Confidence Interval)
Triptans in pregnancy	396	27	0.79 (0.51 to 1.21)	0.78 (0.51 to 1.19)	-0.02 (-0.05 to 0.01)	-0.02 (-0.05 to 0.01)
Vs.Triptans pre-pregnancy only	798	69	Referent	Referent	Referent	Referent
Triptans in pregnancy	396	27	0.88 (0.60 to 1.29)	0.89 (0.61 to 1.30)	-0.01 (-0.04 to 0.02)	-0.01 (-0.03 to 0.01)
Vs. Migraine with no triptan use	3,291	255	Referent	Referent	Referent	Referent
Triptans in pregnancy	396	27	1.09 (0.78 to 1.58)	1.02 (0.71 to 1.47)	0.01 (-0.02 to 0.03)	0.00 (-0.03 to 0.02)
Vs. Population (no triptan use or migraine)	36,688	2284	Referent	Referent	Referent	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSAIDs, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.
2. Marginal structural models weighted with stabilized inverse probability of treatment weights, constructed at each time point using baseline confounders, time-invariant confounders, and medication history.

Table 2.4. (continued)

	Among mothers with migraine (n=4,439)					
	Total N	N with outcome	Crude Risk Ratio (95% Confidence Interval)	Marginal Structural Model Risk Ratio[2] (95% Confidence Interval)	Crude Risk Difference (95% Confidence Interval)	Marginal Structural Model Risk Difference[2] (95% Confidence Interval)
Pre- pregnancy triptan use	1,085	86	1.32 (1.04 to 1.66)	1.04 (0.80 to 1.35)	0.02 (0.00 to 0.04	0.00 (-0.02 to 0.03)
Vs.no pre-pregnancy	3,354	260	Referent	Referent	Referent	Referent
Triptans in 1st trimester	304	20	0.90 (0.54 to 1.48)	1.27 (0.57 to 2.82)	-0.01 (-0.04 to 0.03)	0.02 (-0.06 to 0.10)
Vs. No triptan use in 1st trimester	4,135	326	Referent	Referent	Referent	Referent
Triptans in 2nd /3rd trimester	137	7	0.69 (0.32 to 1.50)	0.70 (0.16 to 3.14)	-0.02 (-0.07 to 0.02)	-0.02 (-0.11 to 0.07)
Vs. No triptan use in 2nd/3rd trimester	4,302	339	Referent	Referent	Referent	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSAIDs, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.
2. Marginal structural models weighted with stabilized inverse probability of treatment weights, constructed at each time point using baseline confounders, time-invariant confounders, and medication history.

Figure 2.1. Inclusion and exclusion of study participants

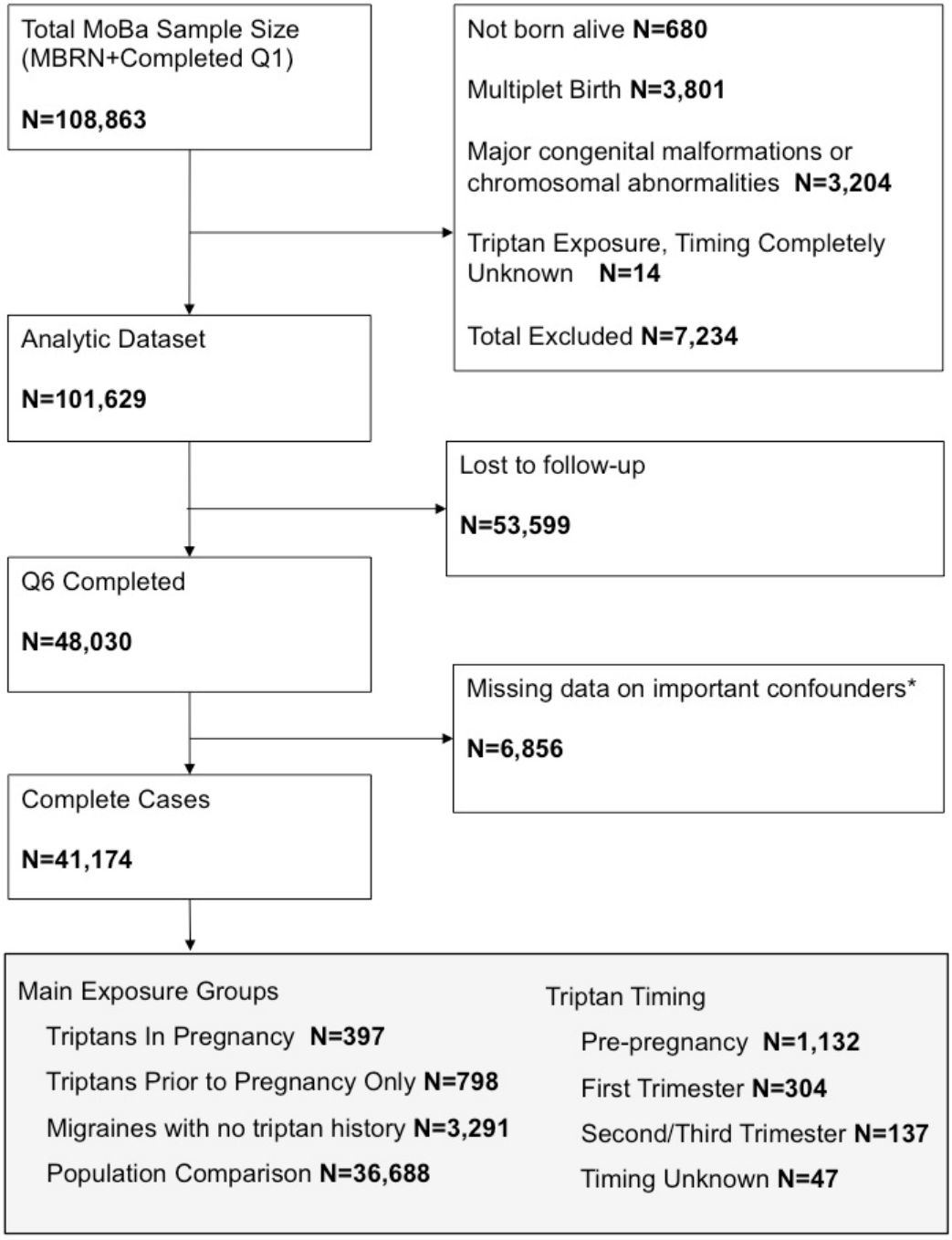
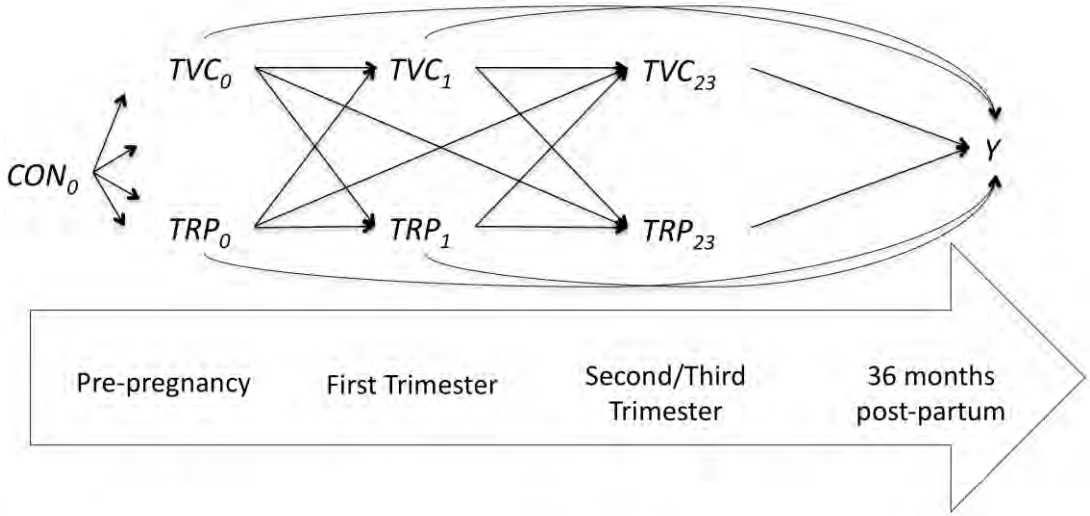


Figure 2.2. Possible causal model for effect of exposure to triptans on neurodevelopmental outcome



KEY: Time-varying exposure and confounding, where TRP_t is triptan medication use at each trimester, CON_0 is the set of measured confounders at baseline, TVC_t are time-varying confounders which include other medication use.

Figure 2.3. Percent of children with clinically-significant behavioral problems in each exposure group

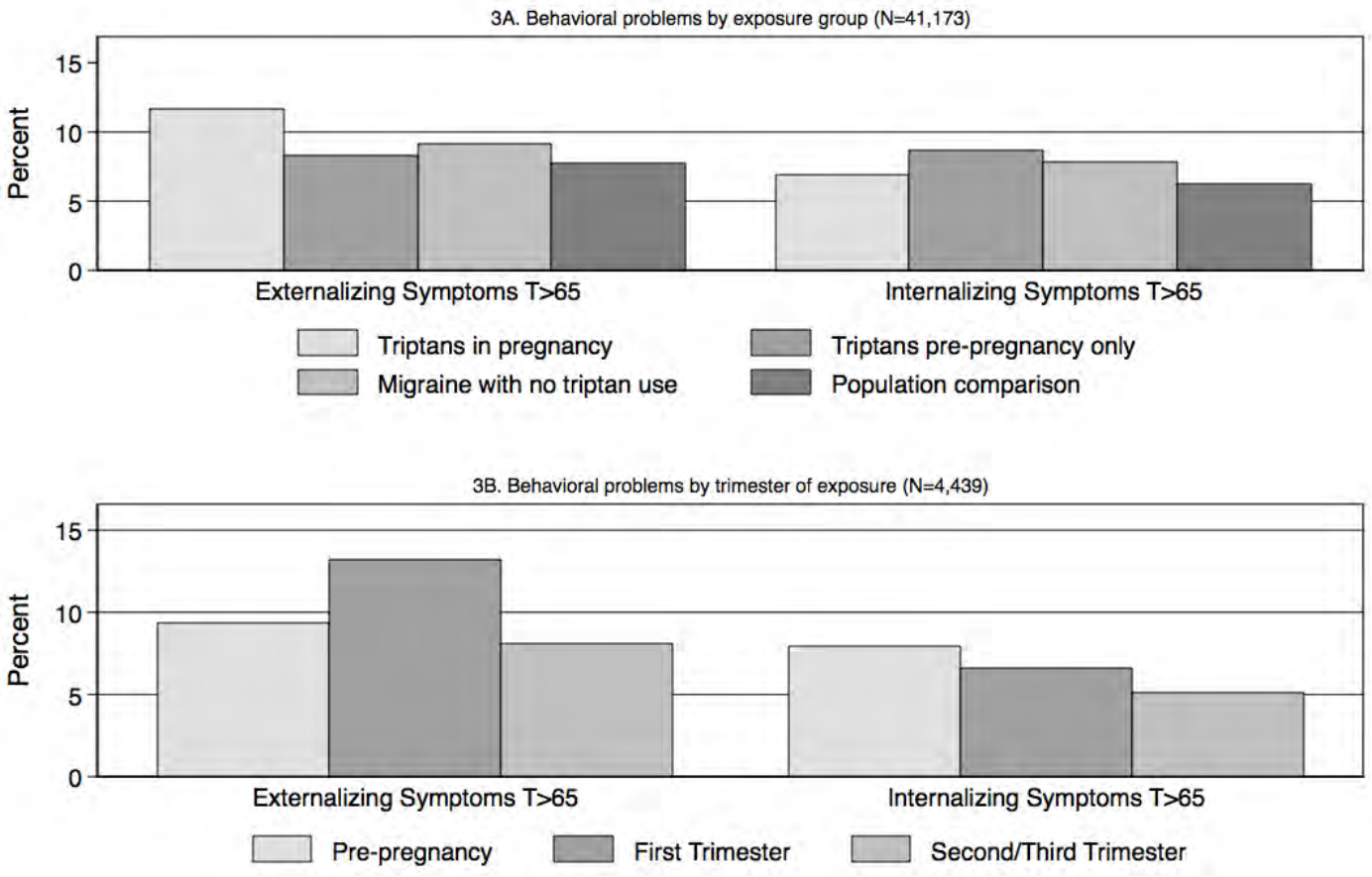


Figure 2.4. Time-varying patterns of medication use

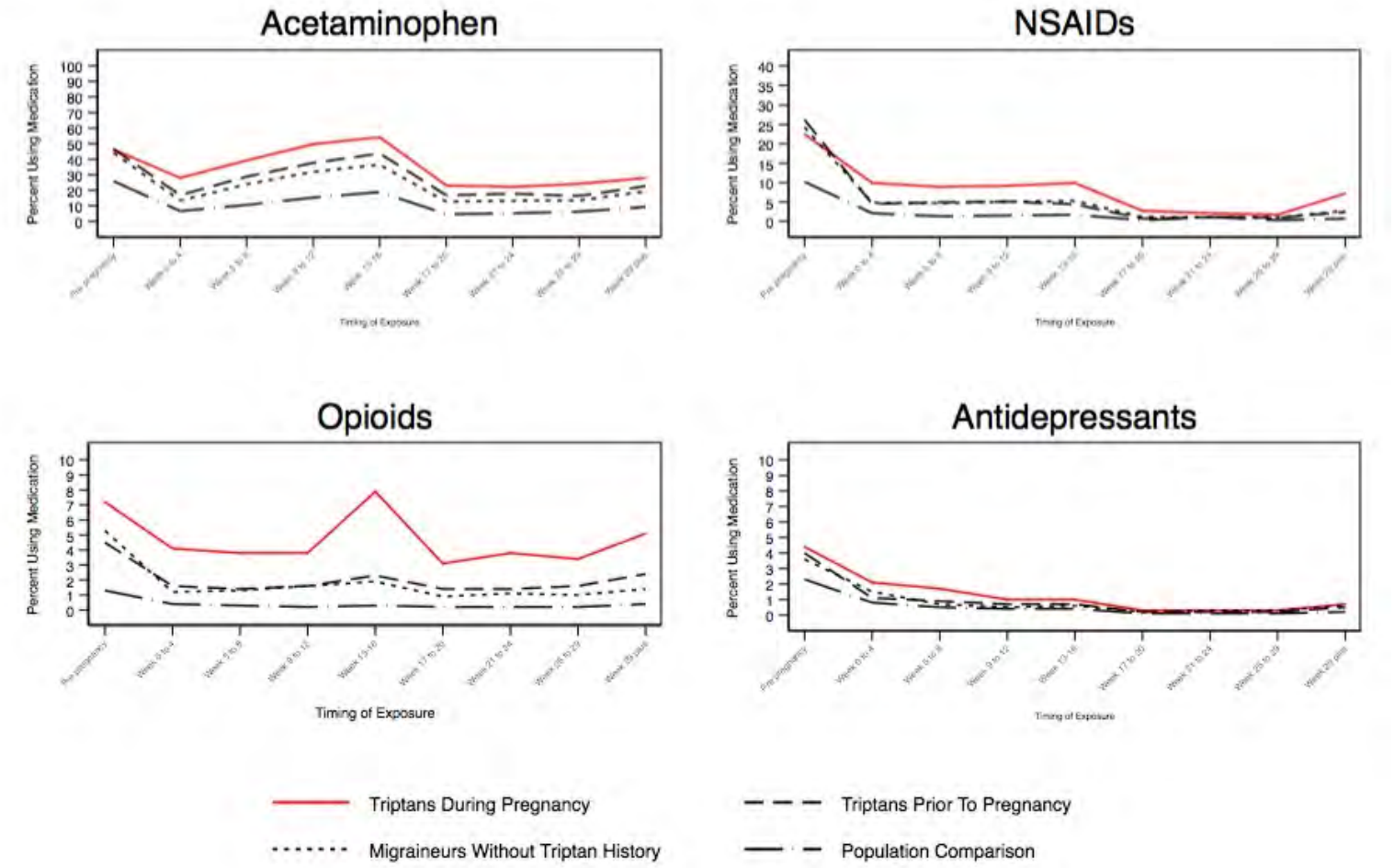


Table 2.S1. Comparison of unadjusted, multivariable adjusted, and marginal structural model estimates of the effect of timing of triptan exposure on behavioral problems (n=4,439)

	Pre-pregnancy use	No pre-pregnancy use	1st trimester use	No use in 1st trimester	2nd or 3rd trimester use	No use in 2nd or 3rd trimester
			Externalizing Problems			
N	1,085	3,354	304	4,135	137	4,302
Number of events	101	297	40	358	11	387
Risk	9.3%	8.9%	13.2%	8.7%	8.0%	9.0%
			Risk Ratios			
Unadjusted	0.94	Referent	1.77	Referent	0.64	Referent
(95% Confidence Interval)	(0.73 to 1.20)		(1.23 to 2.56)		(0.34 to 1.19)	
Multivariable adjusted[1]	0.99	Referent	1.78	Referent	0.63	Referent
(95% Confidence Interval)	(0.78 to 1.27)		(1.24 to 2.56)		(0.34 to 1.15)	
Marginal Structural Model[2]	0.99	Referent	1.75	Referent	0.59	Referent
(95% Confidence Interval)	(0.77 to 1.27)		(0.98 to 3.14)		(0.23 to 1.51)	
			Risk Differences			
Unadjusted	0.00	Referent	0.06	Referent	-0.03	Referent
(95% Confidence Interval)	(-0.01 to 0.02)		(0.01 to 0.10)		(-0.09 to 0.02)	
Multivariable adjusted[1]	0.00	Referent	0.05	Referent	-0.02	Referent
(95% Confidence Interval)	(-0.02 to 0.02)		(0.00 to 0.09)		(-0.08 to 0.04)	
Marginal Structural Model[2]	0.00	Referent	0.06	Referent	-0.04	Referent
(95% Confidence Interval)	(-0.02 to 0.02)		(-0.02 to 0.15)		(-0.09 to 0.01)	

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSA Ds, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.
2. Marginal structural models weighted with stabilized inverse probability of treatment weights, constructed at each time point using baseline confounders, time-invariant confounders, and medication history.

Table 2.S1. (Continued)

	Pre-pregnancy use	No pre-pregnancy use	1st trimester use	No use in 1st trimester	2nd or 3rd trimester use	No use in 2nd or 3rd trimester
			Internalizing Problems			
N	1,085	3,354	304	4,135	137	4,302
Number of events	86	260	20	326	7	339
Risk	7.9%	7.8%	6.6%	7.8%	5.1%	7.9%
			Risk Ratios			
Unadjusted (95% Confidence Interval)	1.32 (1.04 to 1.66)	Referent	0.90 (0.54 to 1.48)	Referent	0.69 (0.32 to 1.50)	Referent
Multivariable adjusted[1] (95% Confidence Interval)	1.27 (1.01 to 1.59)	Referent	0.89 (0.54 to 1.46)	Referent	0.69 (0.32 to 1.49)	Referent
Marginal Structural Model[2] (95% Confidence Interval)	1.04 (0.80 to 1.35)	Referent	1.27 (0.57 to 2.82)	Referent	0.70 (0.16 to 3.14)	Referent
			Risk Differences			
Unadjusted (95% Confidence Interval)	0.02 (0.00 to 0.04)	Referent	-0.01 (-0.04 to 0.03)	Referent	-0.02 (-0.07 to 0.02)	Referent
Multivariable adjusted[1] (95% Confidence Interval)	0.00 (-0.01 to 0.02)	Referent	0.00 (-0.04 to 0.03)	Referent	-0.03 (-0.06 to 0.01)	Referent
Marginal Structural Model[2] (95% Confidence Interval)	0.00 (-0.02 to 0.03)	Referent	0.02 (-0.06 to 0.10)	Referent	-0.02 (-0.11 to 0.07)	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSA Ds, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.
2. Marginal structural models weighted with stabilized inverse probability of treatment weights, constructed at each time point using baseline confounders, time-invariant confounders, and medication history.

Table 2.S2. Additional group-wise comparisons for the risk of externalizing behaviors in disease comparison groups

	Externalizing Symptoms					
	Total N	N with outcome	Crude Risk Ratio (95% Confidence Interval)	Adjusted Risk Ratio[1] (95% Confidence Interval)	Crude Risk Difference (95% Confidence Interval)	Adjusted Risk Difference[1] (95% Confidence Interval)
Triptans pre-pregnancy only	798	66	0.94 (0.73 to 1.22)	0.98 (0.78 to 1.26)	-0.01 (-0.03 to 0.02)	0.00 (-0.02 to 0.02)
Vs. Migraine with no triptan use	3,291	289	Referent	Referent	Referent	Referent
Triptans pre-pregnancy only	798	66	1.07 (0.85 to 1.36)	1.00 (0.79 to 1.26)	0.01 (-0.01 to 0.02)	0.00 (-0.02 to 0.02)
Vs. Population (no triptan use or migraine)	36,688	2,828	Referent	Referent	Referent	Referent
Migraine with no triptan use	3,291	289	1.14 (1.01 to 1.28)	1.02 (0.92 to 1.15)	0.01 (0.00 to 0.02)	0.00 (-0.01 to 0.01)
Vs. Population (no triptan use or migraine)	36,688	2,828	Referent	Referent	Referent	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSAIDs, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.

Table 2.S2. (Continued)

	Internalizing Symptoms					
	Total N	N with outcome	Crude Risk Ratio (95% Confidence Interval)	Adjusted Risk Ratio[1] (95% Confidence Interval)	Crude Risk Difference (95% Confidence Interval)	Adjusted Risk Difference[1] (95% Confidence Interval)
Triptans pre-pregnancy only	798	69	1.12 (0.87 to 1.45)	1.15 (0.89 to 1.47)	0.01 (-0.01 to 0.03)	0.01 (-0.01 to 0.03)
Vs. Migraine with no triptan use	3,291	255	Referent	Referent	Referent	Referent
Triptans pre-pregnancy only	798	69	1.39 (1.10 to 1.75)	1.31 (1.04 to 1.65)	0.02 (0.00 to 0.04)	0.02 (0.00 to 0.04)
Vs. Population (no triptan use or migraine)	36,688	2284	Referent	Referent	Referent	Referent
Migraine with no triptan use	3,291	255	1.24 (1.10 to 1.41)	1.14 (1.01 to 1.30)	0.02 (0.01 to 0.02)	0.01 (0.00 to 0.02)
Vs. Population (no triptan use or migraine)	36,688	2284	Referent	Referent	Referent	Referent

1. Models adjusted for maternal age, pre-pregnancy BMI, parity, marital status, education, cigarette and alcohol use, comedication use (NSAIDs, acetaminophen, opioids, antidepressants), depressive and anxiety symptoms.

Table 2.S3. Bias analysis for the potential impact of confounding by migraine severity on the observed effect estimates for externalizing behavior problems

	Association between migraine severity and outcome (RR_{CD})	Prevalence of severe migraine in triptan users (p1)	Prevalence of severe migraine in triptan discontinuers (p0)	Risk Ratio[1]	95% Confidence Interval
Conventional Result	--	--	--	1.40	0.98 to 2.00
Scenario 1	1.25	0.30	0.15	1.36	0.94 to 1.95
Scenario 2	1.25	0.40	0.20	1.34	0.98 to 2.17
Scenario 3	1.5	0.30	0.15	1.31	0.93 to 1.86
Scenario 4	1.5	0.40	0.20	1.29	0.91 to 1.83
Scenario 5	3.00	0.40	0.20	1.09	0.77 to 1.56
Scenario 6	4.00	0.40	0.20	1.03	0.71 to 1.52

1. Bias-corrected RR based on 10,000 simulations from a uniform distribution

CHAPTER III

PRENATAL TRIPTAN EXPOSURE AND EARLY CHILDHOOD NEURODEVELOPMENTAL OUTCOMES: AN APPLICATION OF PROPENSITY SCORE CALIBRATION TO ADJUST FOR UNMEASURED CONFOUNDING BY MIGRAINE SEVERITY

Title: Prenatal triptan exposure and early childhood neurodevelopmental outcomes: an application of propensity score calibration to adjust for unmeasured confounding by migraine severity

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III.0 Abstract

Background: Triptan medications are serotonin agonists used to treat migraine, a chronic pain condition highly prevalent in women of reproductive age. Data on the safety of triptans during pregnancy are scant. We sought to quantify the association of prenatal triptan exposure on motor function, communication skills, and temperament in three-year-old children.

Methods: Using data from the Norwegian Mother and Child Cohort Study, we used propensity score matching to examine associations between prenatal triptan exposure and psychomotor function, communication, and temperament. We used an external validation study to perform propensity calibration to adjust effect estimates for confounders unmeasured in the main study (migraine severity, type, and maternal attitudes towards medication use).

Results: We identified 4,204 women who reported migraine headache at baseline, of which 375 (8.9%) reported using a triptan ≥ once during pregnancy. Children with prenatal triptan exposure had 1.37-fold greater unadjusted odds of fine motor problems (95% CI: 1.06-1.77), which decreased after propensity score matching (OR: 1.29, 95% CI 0.97-1.73) and was further attenuated after calibration (OR: 1.25, 95%CI 0.89- 1.74). We observed no increased risk for gross motor or communication problems, and no differences in temperament. Adjustment for migraine severity using propensity score calibration had a

substantial impact on effect estimates, with percent changes ranging from 2.4% to 50%.

Conclusions: Prenatal triptan exposure was not associated with psychomotor function, communication problems, or temperament in three-year-old children. Adjustment for migraine severity reduced effect estimates, and should be considered in future studies of the safety of triptans during pregnancy.

III.1 Introduction

Migraine headache is a relapsing-remitting chronic pain condition with a one year prevalence in women of reproductive age of 16-18%.[5,6] The frequency and severity of migraines often changes over the course of pregnancy: 60-70% of women with migraine experience some improvement of symptoms during pregnancy, with 20% of these reporting complete remission. Migraine course during pregnancy tends to be better in women with menstrual migraine as well as in women who have migraines without aura.[6] However, if symptoms do not improve during the first trimester, migraines are likely to continue throughout pregnancy.[6] Given the high prevalence of migraine headache in women of childbearing age, the lack of migraine resolution until after the first trimester, and the high rate of unplanned pregnancy,[4] the potential for early-pregnancy exposure to medications used to treat migraines is high.

Pharmacotherapy for migraine includes both preventive and analgesic medications, and triptans are the most frequently-used prescription medications.[9] Triptans are serotonin 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor agonists that act on the trigeminal cervical complex as well as on smooth muscle; they are taken episodically, as a migraineur feels a migraine attack beginning. There are seven triptans commercially available worldwide: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan.

Ten studies (including more than 6,000 exposed infants) have examined the safety of triptan use during pregnancy on immediate pregnancy outcomes, and have noted no increased risk for major congenital malformations,[12,37,76] although some evidence suggests that triptan use may be associated with pre-eclampsia or preterm birth.[12] In light of the current literature, a recent review of treatment options for pregnant women with migraine, concluded that if acetaminophen was not sufficiently effective, limited use of triptans could be considered during pregnancy, with a preference for sumatriptan.[15]

While several studies focus on the immediate pregnancy outcome following exposure to triptans, the long-term outcomes have received surprisingly limited attention. Triptans readily cross the placenta and the blood-brain barrier and may bind to 5-HT_{1B} and 5-HT_{1D} receptors which are found in fetal brain,[18] and have therefore a biological plausible mechanism for effects on the developing brain. Previously, we evaluated prenatal triptan exposure as a risk factor for internalizing and externalizing behaviors, and found that children exposed prenatally to triptans had a 40% increased risk for clinically-significant externalizing problems; we did not observe an increased risk for internalizing problems.[77] This was the first study on long-term safety of triptans; however, it is unknown whether prenatal exposure to triptans or migraine in itself may increase the risk of other neurodevelopmental outcomes like psychomotor development, temperament and communication.

Building from our previous work, the current study sought to evaluate the effect of in utero exposure to triptans on psychomotor problems and temperamental disturbances. We hypothesized that children born to women who took a triptan medication during pregnancy would have higher rates of psychomotor problems and temperamental disturbances than children unexposed to triptans; we further hypothesized that if these problems were due to the underlying disorder, adjustment for migraine severity would be necessary. Understanding the role of triptans as possible teratogens requires careful consideration of the role of the underlying disease.

III.2 Methods

Norwegian Mother and Child Cohort Study (MoBa) Sample

Between 1999 and 2008, the Norwegian Institute of Public Health invited women to participate in the Norwegian Mother and Child Cohort Study (MoBa). Women were invited prior to their first routine ultrasound appointment (gestational week 13-17). A total of 108,841 women consented to participate (participation rate 42.7%), with 84.8% of the participants completing the six month post-partum questionnaire and 60.2% completing the 36 month post-partum questionnaire.[46,78] Written informed consent was obtained from all participants, and the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study; this analysis was granted an exemption from the University of Massachusetts Medical School Institutional

Review Board. Data were taken from the quality-ensured Data Version 6, released by MoBa in 2012 and includes all children born before 2009 for whom the age three years questionnaire was received by May 4, 2011; these data were linked to the Medical Birth Registry of Norway (MBRN) using participants' 11-digit personal identification numbers. Figure 3.1 shows the exclusion criteria and the development of the analysis sample (n=4,204).

Ascertainment of triptan exposure

Information on exposure to medications was gathered prospectively from two prenatal (Q1-gestational week17, Q3-gestational week 30) and one postpartum questionnaire (Q4-6 months post partum). Women were asked to indicate when they had taken a medication (during the six months before pregnancy, during weeks 0-4, 5-8, 9-12, and/or 13 or later for Q1, during weeks 13-16, 17-20, 21-24, 25-28, and/or week 29 or later for Q3, and from week 30 until birth for Q4), and to write the name of the medication in a text box. Women who indicated multiple medications in a single text box (e.g., sumitriptan and acetaminophen) were assumed to have been exposed to all listed medications in all time periods. No information was available on formulation or dose. Exposure was categorized into two indicator variables: triptan use during pregnancy (yes or no) and triptan use prior to pregnancy (yes or no).

Ascertainment of outcome

To build on previous work examining the effect of prenatal triptan exposure on internalizing and externalizing symptoms, we chose two domains of neurodevelopment: temperament and psychomotor function.

Emotionality, Activity, and Shyness Temperament Questionnaire (EAS)

The Emotionality, Activity, and Shyness Temperament Questionnaire measures four temperament domains (emotionality, shyness, sociability, and activity). A substantial body of literature has linked early childhood temperament to later life depression and other psychiatric diagnoses.[79,80] The shortened version of the EAS used in the MoBa study, was developed with Norwegian social norms in mind, and includes 12 descriptions (e.g. “Your child likes to be with people;” “Your child cries easily.”), and parents are asked to rate how well each statement applies to their child; in a Norwegian sample, the four factor structure of the original scale was reproduced, and internal consistency within each scale ranged from α=0.48 to α=0.79. [81] We calculated z-scores based on the sample distribution of each domain. Higher z-scores indicate greater parental endorsement of each temperament trait (e.g. more shy, or more sociable) relative to parental reports of other children in the sample.

Ages and Stages Questionnaire (ASQ)

The Ages and Stages Questionnaire is a parent-completed questionnaire appropriate for children aged four months to five years. Deficits detected by the ASQ have been shown to be predictive of school difficulties in older children,[82] and fine motor skills are highly predictive of later academic achievement.[83] The

abbreviated ASQ used in MoBa includes questions about developmental milestone attainment in three major categories: gross motor, fine motor, and communication; this shortened version has been validated in a Norwegian population, and had excellent test-retest reliability (94%) and agreement between parents and professional examiners, as well as acceptable sensitivity and specificity (72% and 86%, respectively)[84]. We categorized each domain of the ASQ to indicate whether a child had a delay in at least one motor skill or at least two communication skills assessed, identified by a parent reporting "Not yet" (versus "Yes" or "Sometimes").

Concomitant medication use

We examined other pain medications and psychotropic medications as potential confounders, using the following ATC codes: N02BE01 (acetaminophen), N02A (opioids), M01A (non-steroidal anti-inflammatory drugs, NSAIDs), N06A (antidepressants), N05CD02, N05CD03, N05CD08, N05BA01, N05BA05, N05BA12 (benzodiazepines), and N03A (anti-convulsants). All co-medications were categorized as ever vs. never used in pregnancy and prior to pregnancy.

Potential confounders

Maternal age, pre-pregnancy body mass index (BMI) (underweight or <18.5 kg/m^2, normal weight or 18.5-25 kg/m^2, or overweight, >25 kg/m^2 according to WHO guidelines), education (primary or secondary vs university or higher), marital status (married or cohabiting vs other), parity (multiparous vs.

primiparous) and depression history (yes or no) were all ascertained by self-report on Q1. Smoking (ever during pregnancy vs. not during pregnancy) and alcohol use (ever during pregnancy vs. not during pregnancy) were ascertained by combining information from self-report and linkage to the Medical Birth Registry of Norway.

MIMEGA Migraine sample description

Women with migraine who were ≥ 18 years of age and who were currently pregnant or had a child <18 months old were invited to participate in the MIMEGA migraine study[85] from October 2013-January 2014. Recruitment was done by the Oslo Migraine Clinic and the Norwegian Migraine Association, in addition to advertisements on websites for pregnant women and new mothers and on the study's Facebook page. Women filled out an anonymous electronic questionnaire developed using the Online Forms Service of the University of Oslo (http://www.nettskjema.uio.no/). The Regional Committee for Medical and Health Research Ethics (Region North) approved the study, and informed consent was obtained (n=380). The MIMEGA study includes important information on migraine type, severity, and beliefs about medication use, which were not assessed in the main MoBa study.

Women self-reported their age, gestational week (if pregnant) or age of child (if post-partum), education (primary or secondary vs university or higher), marital status (married or cohabiting vs other), parity (multiparous vs. primiparous) smoking and alcohol use during pregnancy (any use after learning

she was pregnant vs. no use), and use of other medications (including triptans, acetaminophen, NSAIDs, and opioids).

Women were asked about the severity of migraine attacks during pregnancy using the Migraine Severity Scale [86], a four item questionnaire that assessed pain severity, tolerance, nausea, and impairment of daily activity due to migraine. Scores range from 0 to 15, and higher scores indicate more severe migraine. The Beliefs About Medications Questionnaire (BMQ) [87,88] includes 10 statements designed to assess patients' concerns about medications and their views on medication necessity. The BMQ includes two subscales: the BMQ-Necessity and the BMQ-Concerns, each with five items; respondents indicate their agreement with each item (1=strongly disagree, 5=strongly agree), and individual items are summed to produce a total score which ranges from 5-25, with higher scores indicating greater belief in the concepts represented by the subscale (concerns about medications or greater perceived need of medications, respectively).

Statistical Analysis

We began analysis by estimating the prevalence of triptan exposure during pregnancy, and then obtaining descriptive statistics for the sample (collectively and by prenatal triptan exposure). Four modeling approaches were used to provide: 1) multivariable adjusted estimates; 2) propensity score matched estimates; 3) propensity score adjusted estimates; and 4) propensity score calibration estimates.

We modeled the EAS temperament outcomes by fitting general linear models and the ASQ delay outcomes by fitting logistic models. Other functional forms of the generalized linear model, including Poisson models, were assessed and compared using goodness-of-fit metrics and visual inspection of data. For both outcomes, we followed the similar model-building strategies. We began with an unadjusted model in which triptan use in pregnancy was the only variable. Then, we added potential confounders into the model singly to assess the extent to which each confounder changed the measure of association between triptan use in pregnancy and the outcome variable. The final set of confounders used in all models was selected from a combination of literature review, iterative use of directed acyclic graphs, and substantial (>10%) change in the measure of association for the triptan variable (indicating material confounding), and included: maternal age, pre-pregnancy BMI, marital status, maternal education, smoking or alcohol use during pregnancy, presence of maternal depression, use of triptans prior to pregnancy, and concomitant medication use during pregnancy (acetaminophen, NSAIDs, opioids, antidepressants).

Propensity score methods remove substantial bias in effect estimates that arise from measured differences between the exposed and unexposed groups, and assuming no unmeasured confounding, allow us to estimate causal effects. We used logistic regression in which prenatal triptan exposure was the outcome variable and the variables previously selected as material or theoretical confounders during multivariable model building were predictors. Our propensity

score model had a c-statistic of 0.86, and visual inspection of the propensity score distribution showed substantial overlap between the exposed and unexposed women. We implemented propensity score matching without replacement using *psmatch_multi*, a SAS macro that uses local matching to retain matches for the exposed units with the least number of possible matches first; we performed a 1:2 match, selecting two unexposed women for every exposed individual, with non-replacement and a caliper of 0.10. To asses whether matching on the propensity score had produced comparable groups, we used logistic regression to determine whether the measured confounders in our study predicted triptan exposure in the matched sample; the c-statistic was 0.57, suggesting that the matched cohort was relatively balanced with respect to measured confounders. We also compared the characteristics of the exposed and unexposed women in the matched sample. We then compared the neurodevelopmental outcome measures (EAS and ASQ subscales) using general linear models for the continuous EAS outcomes and logistic regression for the categorical ASQ outcomes. These analyses included covariates that remained unbalanced after propensity matching.

We estimated an effect from the full sample with propensity score included as a covariate. Although adjustment for propensity score is not the optimal use of propensity score methods, adjustment for propensity score yields more stable estimates than multivariable adjustment, in the case of a rare exposure and a complex model with many predictors; in addition, these estimates were

compared with propensity-calibrated estimates to better understand the potential impact of unmeasured confounders.

Stabilized Inverse Probability of Censoring Weights

To address differential loss to follow up by triptan use (Figure 3.1), we identified factors associated with attrition, and created stabilized inverse probability of censoring weights (IPCW) using logistic regression.[62] The censoring weight included maternal age, pre-pregnancy BMI, marital status, education, reproductive history, depression, concomitant medication use, and use of triptans prior to and during pregnancy. This method ensures balance of measured predictors of attrition, which reduces selection bias.

Propensity score calibration

The MoBa study did not include information on several potentially important confounders for this study question, including migraine type, migraine severity, concerns about medications, and belief in the necessity of medications. To adjust for these unmeasured confounders, we implemented a method first described by Sturmer et al [89], which combines propensity score adjustment with regression calibration using an external validation study. To implement propensity score calibration, we first estimated an "error-prone" propensity score in the MIMEGA sample using only the confounders available in both the MoBa sample and the MIMEGA sample: age, education, marital status, parity, smoking or alcohol use during pregnancy, history of depression, use of triptans prior to

pregnancy, and concomitant medication use during pregnancy (opioids, acetaminophen, NSAIDs). Next, we estimated a "gold standard" propensity score in the MIMEGA study using predictors available in MoBa and predictors unmeasured in Moba but available in our external validation sample, including migraine type, severity, and medication attitudes. The c-statistics for the error-prone propensity score model and gold-standard propensity score model were 0.81 and 0.87, respectively, indicating that the addition of information from the new predictors improved the gold-standard PS. Because regression calibration may fail in the presence of extreme measurement error (in this case, if the error-prone PS and gold standard PS widely diverged), we estimated the correlation between the two propensity scores and found it to be acceptable (r=0.81-0.89). Finally, we used a freely available SAS macro (available at http://www.hsph.harvard.edu/donna-spiegelman/software/blinplus-macro/) to calibrate the error-prone PS estimated in MoBa using regression parameters obtained in the external validation study, and calculated the percent change (calculated as [($PSC_{adjusted}$ – $PS_{adjusted}$) / $PSC_{adjusted}$] *100) from the PS-adjusted models to the PS-adjusted and calibrated models, to understand the magnitude of the impact that confounding by migraine type, severity, and medication attitudes may have had on our effect estimates.

III.3 Results

MoBa Sample Description

Of the 4,204 women included in this study, 25.4% reported use of triptans in the six months prior to pregnancy and 8.9% used a triptan at least once during pregnancy. Among prenatal triptan users, 77.4% used during the first trimester, 34.1% during the second and third trimesters, and 11.5% reported triptan use during pregnancy but did not report timing of exposure. Women who took a triptan during pregnancy more often had a history of triptan use prior to pregnancy, and during pregnancy, were more likely to have used opioids, acetaminophen, and NSAIDs than those who did not. Women who used triptans during pregnancy were more likely to drink alcohol than those who did not. Rates of concomitant medication use were higher among women who used triptans during pregnancy, while women who did not use triptans prior to pregnancy more often discontinued use of other medications. After propensity score matching, balance improved between exposed and unexposed groups on pre-pregnancy use of medications triptans and opioids, and alcohol using during pregnancy; use of opioids and NSAIDs during pregnancy remained somewhat unbalanced after matching (Table 3.1).

MIMEGA Calibration Sample Description

Among women who participated in the MIMEGA study (n=380), 12.1%, reported triptan use during their pregnancy. Triptan users were more likely than non-users to report depression, were overwhelmingly more likely to have taken triptans prior to pregnancy, and had far higher rates of use of opioids, acetaminophen and NSAIDs during pregnancy. Women who reported taking a

triptan during pregnancy reported higher migraine severity, were more likely to believe migraine medications were necessary, and showed higher levels of concern about using migraine medications than women who did not take triptans during pregnancy. Prenatal triptan users were also more likely to report having migraine without aura and less likely to be unsure about their type of migraine than women who did not report triptan use during pregnancy (Table 3.2).

Comparison of MoBa and MIMEGA samples

Comparing the characteristics of the MoBa and MIMEGA samples revealed several differences, particularly in education, rates of cigarette and alcohol use in pregnancy, rate of folate supplementation, and rate of other medication use prior to and during pregnancy (Table 3.2). However, when we examined the associations between individual confounders and use of triptans during pregnancy for the MoBa and calibration studies, we found that maternal age and use of opioids, acetaminophen, and NSAIDs during pregnancy were similarly associated with triptan use during pregnancy, as was pre-pregnancy triptan use and pre-pregnancy opioid use, albeit with some differences in point estimates and wider 95% confidence intervals owing to the differences in sample sizes. Migraine severity was associated with triptan use in pregnancy, as were beliefs about medication necessity and concerns about medication use; migraine type was not associated with triptan use (Table 3.3).

Main Outcome Analysis

Ages and Stages Questionnaire

In the MoBa sample, 2.5% of children had a gross motor delay, 18.0% had a fine motor delay, and 1.3% had a communication delay. Unadjusted estimates for fine motor delays suggested an increased risk associated with prenatal triptan exposure (Odds Ratio (OR) 1.37, 95% Confidence Interval (CI): 1.06 to 1.77), which was reduced after propensity matching (OR 1.29, 95% CI: 0.94 to 1.76); multivariable and propensity adjustment attenuated this risk. No association was observed between prenatal triptan exposure and gross motor or communication delays (Table 3.4).

Emotionality, Activity, and Shyness Temperament Questionnaire

Before adjustment, children exposed to triptans during fetal development had slightly higher mean shyness (β 0.08, 95%CI -0.04 to 0.19); adjustment for propensity for triptan use, however, moved estimates closer to the null (β 0.05, 95%CI -0.07 to 0.18). No association was observed between triptan exposure and sociability, emotionality, or activity (Table 3.4).

Sensitivity Analysis: Propensity score calibration

To consider confounding by migraine type, severity, and medication attitudes, we performed propensity-score calibrations. In most cases, PS-calibrations either moved point estimates closer to zero, with percent differences ranging from 8.8-50% relative to PS-adjusted models (EAS Sociability, Activity, and Shyness Scales; ASQ Fine Motor and Communication delays), suggesting that some unmeasured confounding by migraine type, severity, and medication attitudes was present in the traditional PS-adjusted effect estimates (Table 3.5).

III.4 Discussion

Within the 10.9% of women in the MoBa study who reported migraine headache at baseline, 8.9% used a triptan medication at least once during pregnancy, which underscores the need for more information about the safety of these medications during pregnancy. The current study found no association between prenatal exposure to triptans and motor delays, communication delays, or temperament, after adjustment for measured confounders and calibration for unmeasured confounders. Fine motor delays were relatively common (18% of sample) while gross motor and communication delays were rare (2.5% and 1.3%, respectively), which is not unexpected given the age of assessment. Mean temperament scores were variable, but covered the range of scores found in the larger MoBa study.

These findings contrast with our previous work, which noted an increased risk of externalizing behaviors in children exposed to triptans during fetal development.[77] One possible explanation for these differences is that externalizing behaviors, motor and communication skills, and temperament are associated with different brain regions, which may be differentially sensitive to teratogens during development: further study is needed to better understand these vulnerabilities and their potential neurodevelopmental consequences.

There may be other explanations for the lack of observed association between prenatal triptan exposure and psychomotor problems or temperament. Because triptan use in pregnancy is a relatively rare in the MoBa cohort, we may have failed to detect differences between exposed and unexposed groups due to lack of power. For continuous outcomes, this study had adequate power to detect moderate effects, or effect sizes of d=0.20 or greater. For categorical outcomes, however, the study had sufficient power to detect an odds ratio of 1.7 or greater, suggesting that for gross motor and communication problems, we may have failed to detect more subtle effects. It is also possible that the null result we observed could be due to non-differential misclassification of exposure. Techniques to adjust for non-differential misclassification using propensity score methods are (to our knowledge) unavailable.

We hypothesized that migraine characteristics, including severity, would be associated with a woman's likelihood of taking a triptan during pregnancy. Migraine itself is associated with adverse pregnancy outcomes, including hypertensive disorders, preterm birth[90,91] and low birth weight,[90] and increased risk of neurodevelopmental problems in children exposed *in utero.*[68] This study provides evidence that migraine severity and medication beliefs were associated with triptan use in pregnancy. Independent of medication use, migraine severity in particular may also be associated with child neurodevelopment: chronic pain is related to increased stress response, which in turn is associated with neurodevelopmental problems in children.[92] We found that adjusting for migraine

severity did influence our observed effect estimates, even within the context of a null study. Failing to appropriately consider these facets of the underlying indication for which the triptan medication is used could lead to overestimating the risk of prenatal triptan exposure. This underlines the need for studies of medication use during pregnancy to carefully consider the role of the underlying medical condition for which the medication was prescribed in any findings.

Our study had several important limitations. The MoBa study did not collect information on migraine type or severity, and results from our propensity calibration analysis suggest that adjustment for these factors tended to move effect estimates towards the null. We used the MIMEGA study to apply propensity score calibaration. The MIMEGA sample was recruited as many as 10 years after the MoBa sample, and may be different from the MoBa sample in multiple ways, including education, severity, or concern about medication safety. The propensity score calibration is dependent on an assumption of surrogacy, which states that the error-prone propensity score in the main MoBa study is independent of the outcome given the gold-standard propensity score in the validation study.[93] Neurodevelopmental outcomes were not measured in the MIMEGA study, and so the surrogacy assumption is not verifiable. However, we hypothesized that the direction of confounding was similar for the variables measured in the MIMEGA and MoBa studies, and so should not result in a violation of surrogacy.[94]

Despite these limitations, this study makes several important contributions. First, the study is set in the Norwegian Mother and Child Cohort Study, a prospective birth cohort in which information on medication exposure was gathered prior to observing any neurodevelopmental outcomes and therefore minimizing the potential for differential information bias. We applied multiple methodological techniques to minimize, assess, and where possible, reduce bias due to measured and unmeasured confounders. Women who took triptans during pregnancy were different from those who did not in a variety of ways, including the number of concomitant medications taken, history of depression, and alcohol use during pregnancy, as well as migraine severity and attitudes towards medication use: failure to adequately consider these confounders could have led us to attribute teratogenic effects to triptans that might be more properly attributed to underlying disease severity.

Our prior work identified increased risks of externalizing behaviors associated with prenatal triptan exposure; the current study, focusing on temperament, psychomotor problems, and communication problems revealed no differences between children with and without prenatal triptan exposure. Taken together, the evidence so far is not sufficient to recommend changes to guidelines for use of triptans during pregnancy, which currently suggest that these medications may be used conservatively. Future studies should take into account migraine severity when considering the possible effects of prenatal exposure to triptan medications.

Table 3.1. Maternal characteristics and medication use among women with history of migraine headache in the Norwegian Mother and Child Cohort Study (MoBa), before and after propensity score matching

	Full Sample		Propensity-Matched Sample	
	Triptans In Pregnancy	No Triptans In Pregnancy	Triptans In Pregnancy	No Triptans In Pregnancy
	N=375	N=3,829	N=365	N=730
Age in years (Mean, SD)	30.9(4.3)	30.3(4.4)	30.8(4.3)	30.8(4.1)
BMI (kg/m^2)				
<18.5	2.7[1]	3.5	2.7	2.6
18.5-25	60.3	61.6	60.0	62.2
>25	37.1	34.9	37.3	35.2
Multiparous	47.7	51.8	48.0	47.5
Married or cohabitating	95.5	97.2	95.9	97.0
Mother Education				
Primary or secondary	30.1	35.6	30.4	29.6
University or higher	69.9	64.4	69.6	70.4
Smoking during pregnancy	11.7	12.7	11.8	11.9
Alcohol during pregnancy	20.3	15.2	19.5	18.0
Folate Supplementation	60.8	58.8	60.8	62.1
Medications Taken In Pregnancy				
Opioids	12.8	4.8	10.4	6.1
Acetaminophen	76.0	65.0	75.3	73.6
NSAIDs	22.4	12.1	20.8	13.2
Anticonvulsants	0.3	0.3	0.3	0.1
Antidepressants	1.6	1.5	1.6	1.2
Benzodiazepines	1.6	0.5	1.4	0.7
Medications Before Pregnancy				
Triptans	84.0	19.7	83.6	83.4
Opioids	7.7	15.1	6.9	6.4
Acetaminophen	46.1	45.4	45.8	48.1
NSAIDs	21.9	23.8	20.8	25.5
Anticonvulsants	0.5	0.3	0.6	0.3
Antidepressants	5.1	3.9	5.2	4.7
Benzodiazepines	1.3	1.0	1.6	1.5
Maternal Depression	12.3	12.2	12.3	12.6

1. Values reported are column percents; age is reported as mean(standard deviation)

Table 3.2. Maternal characteristics and medication use among women with history of migraine headache, full sample and calibration sample

	MoBa Study		MIMEGA Study	
	Triptans In Pregnancy	No Triptans In Pregnancy	Triptans In Pregnancy	No Triptans In Pregnancy
	N=375	N=3,829	N=46	N=334
Age in years (Mean, SD)	30.9(4.3)	30.3(4.4)	31.5(5.9)	30.7(4.9)
BMI (kg/m^2)				
<18.5	2.7	3.5	--	--
18.5-25	60.3	61.6	--	--
>25	37.1	34.9	--	--
Multiparous	47.7	51.8	69.6	82.6
Married or cohabitating	95.5	97.2	93.5	95.2
Mother Education				
Primary or secondary	30.1	35.6	67.4	75.5
University or higher	69.9	64.4	32.6	24.6
Smoking during pregnancy	11.7	12.7	8.7	6.6
Alcohol during pregnancy	20.3	15.2	8.7	1.8
Folate Supplementation	60.8	58.8	89.1	86.5
Medications Taken In Pregnancy				
Opioids	12.8	4.8	23.9	9.3
Acetaminophen	76.0	65.0	78.3	65.3
NSAIDs	22.4	12.1	23.9	6.0
Anticonvulsants	0.3	0.3	--	--
Antidepressants	1.6	1.5	--	--
Benzodiazepines	1.6	0.5	--	--
Medications Before Pregnancy				
Triptans	84.0	19.7	97.8	61.7
Opioids	7.7	5.1	21.7	18.3
Acetaminophen	46.1	45.4	73.9	65.0
NSAIDs	21.9	23.8	60.9	58.1
Anticonvulsants	0.5	0.3	--	--
Antidepressants	5.1	3.9	--	--
Benzodiazepines	1.3	1.0	--	--
Maternal Depression	12.3	12.2	8.7	4.2
Migraine Type				
With Aura	--	--	37.0	42.8
Without Aura	--	--	43.5	31.7
Other/Do not know	--	--	19.6	25.5
Migraine Severity Score (MIGSEV) (Mean, SD)	--	--	12.0(2.6)	9.1(4.7)
Beliefs About Medicines Questionnaire (BMQ): Necessity Subscale (Mean, SD)	--	--	18.1(4.0)	13.9(5.0)
Beliefs About Medicines Questionnaire (BMQ): Concern Subscale (Mean, SD)	--	--	15.4(4.2)	13.5(4.5)

1. Values reported are column percents; age, Migraine Severity Score, and Beliefs About Medicines Questionnaire are reported as mean (standard deviation)

Table 3.3. Propensity for use of triptans in pregnancy for the main ("MoBa") study and the external validation study ("MIMEGA")

	MoBa Study		MIMEGA Study	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age in years[1]	1.0	1.0 to 1.1	1.0	1.0 to 1.1
BMI (kg/m^2)				
<18.5	0.8	0.4 to 1.5	--	--
18.5-25	REF		--	--
>25	1.1	0.9 to 1.4	--	--
Multiparous	0.9	0.7 to 1.1	0.5	0.2 to 1.0
Married or cohabitating	0.6	0.4 to 1.0	0.7	0.2 to 2.6
Mother Education				
University or higher vs. other categories	0.8	0.6 to 1.0	1.5	0.8 to 2.9
Smoking during pregnancy	0.9	0.7 to 1.3	1.4	0.4 to 4.1
Alcohol during pregnancy	1.4	1.1 to 1.9	5.2	1.4 to 19.2
Folate Supplementation	1.1	0.9 to 1.4	1.3	0.5 to 3.4
Medications Taken In Pregnancy				
Opioids	2.9	2.1 to 4.1	3.1	1.4 to 6.6
Acetaminophen	1.7	1.3 to 2.2	1.9	0.9 to 4.0
NSAIDs	2.1	1.6 to 2.7	4.9	2.2 to 11.1
Anticonvulsants	0.9	0.1 to 6.6	--	--
Antidepressants	1.1	0.5 to 2.6	--	--
Benzodiazepines	2.6	1.0 to 6.9	--	--
Medications Before Pregnancy				
Triptans	21.4	16.1 to 28.5	27.9	3.8 to 204.9
Opioids	1.5	1.0 to 2.3	1.2	0.6 to 2.6
Acetaminophen	1.0	0.8 to 1.3	1.5	0.8 to 3.1
NSAIDs	0.9	0.7 to 1.2	1.1	0.6 to 2.1
Anticonvulsants	1.9	0.4 to 8.4	--	--
Antidepressants	1.3	0.8 to 2.1	--	--
Benzodiazepines	1.6	0.7 to 3.8	--	--
Maternal Depression	1.0	0.7 to 1.4	2.2	0.7 to 6.9
Migraine Type				
With Aura vs Other/Don't know	--	--	1.1	0.5 to 2.6
Without Aura vs Other/Don't know	--	--	1.8	0.8 to 4.1
Migraine Severity Score (MIGSEV) [1]	--	--	1.2	1.1 to 1.4
Beliefs About Medicines Questionnaire (BMQ): Necessity Subscale [1]	--	--	1.2	1.1 to 1.3
Beliefs About Medicines Questionnaire (BMQ): Concern Subscale [1]	--	--	1.1	1.0 to 1.2

1. Odds of triptan use in pregnancy associated with a one-unit increase in age, MIGSEV score or BMQ score

Table 3.4. Comparison of associations between prenatal triptan exposure and neurodevelopmental outcome observed with multivariable adjusted, propensity adjusted, and propensity matched models

	β[1]	95% Confidence Interval
Emotionality, Activity, and Shyness Questionnaire (EAS)		
EAS Sociability		
Unadjusted (MoBa study only)	0.04	-0.07 to 0.15
Multivariable-adjusted (MoBa study only)[2]	0.02	-0.10 to 0.14
PS-adjusted (MoBa study only)[3]	0.02	-0.10 to 0.14
PS-matched (MoBa study only)[4]	0.02	-0.11 to 0.15
EAS Emotionality		
Unadjusted (MoBa study only)	-0.02	-0.14 to 0.10
Multivariable-adjusted (MoBa study only)[2]	0.00	-0.13 to 0.13
PS-adjusted (MoBa study only)[3]	-0.01	-0.14 to 0.12
PS-matched (MoBa study only)[4]	-0.04	-0.18 to 0.09
EAS Activity		
Unadjusted (MoBa study only)	0.06	-0.06 to 0.17
Multivariable-adjusted (MoBa study only)[2]	0.03	-0.09 to 0.16
PS-adjusted (MoBa study only)[3]	0.03	-0.09 to 0.16
PS-matched (MoBa study only)[4]	0.05	-0.09 to 0.18
EAS Shyness		
Unadjusted (MoBa study only)	0.08	-0.04 to 0.19
Multivariable-adjusted (MoBa study only)[2]	0.05	-0.07 to 0.18
PS-adjusted (MoBa study only)[3]	0.05	-0.07 to 0.18
PS-matched (MoBa study only)[4]	0.09	-0.04 to 0.22
Ages and Stages Questionnaire (ASQ)	Odds Ratio[1]	95% Confidence Interval
ASQ Gross Motor Problems		
Unadjusted (MoBa study only)	0.44	0.16 to 1.20
Multivariable-adjusted (MoBa study only)[2]	0.42	0.15 to 1.18
PS-adjusted (MoBa study only)[3]	0.46	0.16 to 1.31
PS-matched (MoBa study only)[4]	0.54	0.18 to 1.61
ASQ Fine Motor Problems		
Unadjusted (MoBa study only)	1.37	1.06 to 1.77
Multivariable-adjusted (MoBa study only)[2]	1.29	0.97 to 1.72
PS-adjusted (MoBa study only)[3]	1.29	0.97 to 1.73
PS-matched (MoBa study only)[4]	1.29	0.94 to 1.76
ASQ Communication Problems		
Unadjusted (MoBa study only)	1.22	0.52 to 2.88
Multivariable-adjusted (MoBa study only)[2]	0.96	0.37 to 2.46
PS-adjusted (MoBa study only)[3]	1.02	0.41 to 2.53
PS-matched (MoBa study only)[4]	0.78	0.28 to 2.14

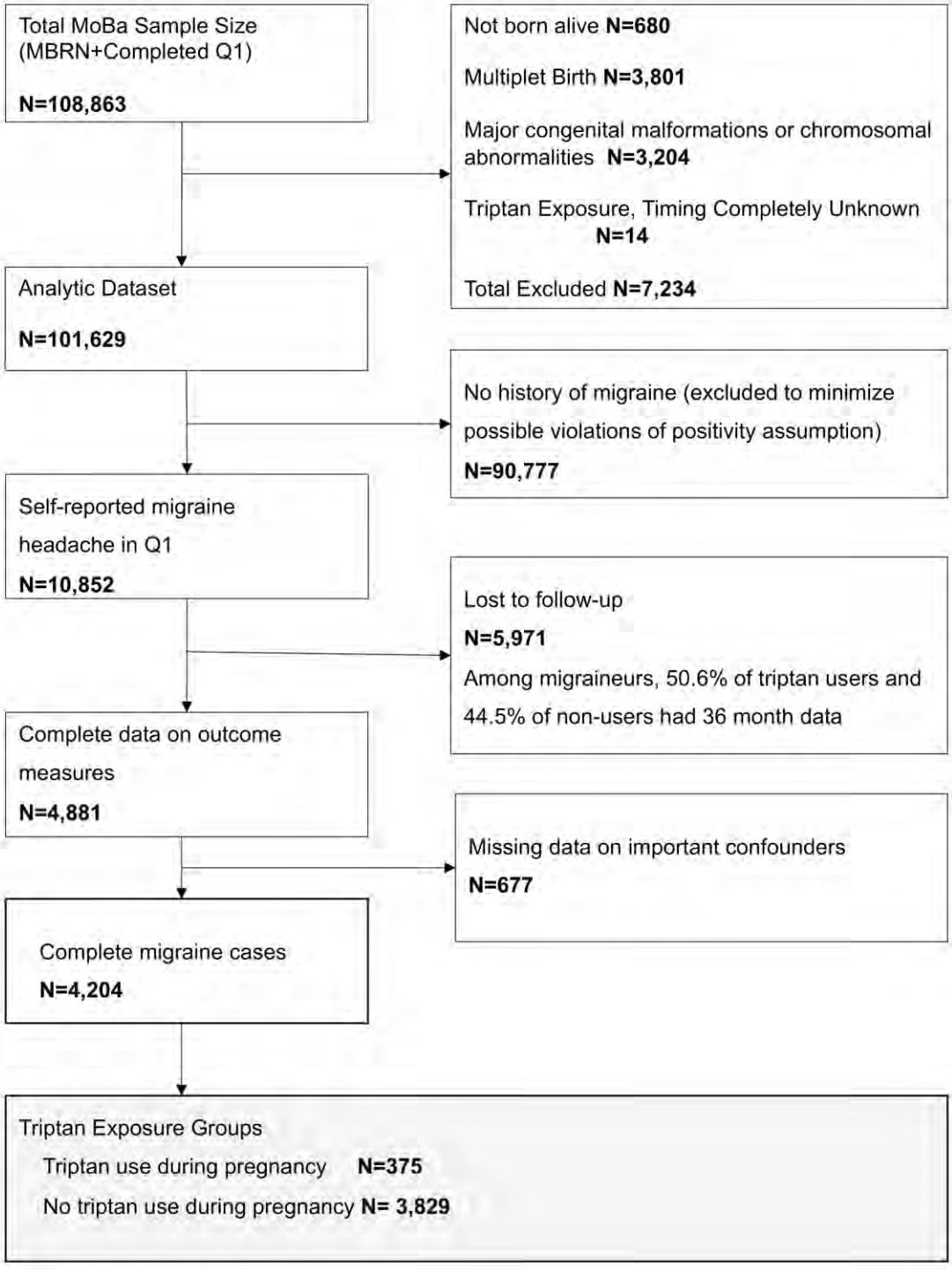
1. β is the change in standard deviation units associated with triptan exposure during fetal development, compared to no triptan exposure; Odds Ratio is the odds of having one or more delay in each domain associated with triptan exposure, relative to no exposure.
2. Adjusted for maternal age, pre-pregnancy BMI, reproductive history, marital status, maternal education, smoking or alcohol use during pregnancy, presence of depressive symptoms, pre-pregnancy triptan use, and co-medication use during pregnancy (acetaminophen, opioids, NSAIDs, antidepressants)
3. Adjusted for the propensity for taking triptans during pregnancy, conditional on maternal age, pre-pregnancy BMI, reproductive history, marital status, maternal education, smoking or alcohol use during pregnancy, presence of depressive symptoms, pre-pregnancy triptan use, and co-medication use during pregnancy (acetaminophen, opioids, NSAIDs, antidepressants)
4. Each exposed triptan user was matched to two non-users based on propensity score; models were further adjusted for factors that remained unbalanced after matching (pregnancy use of opioids and NSAIDs)

Table 3.5. Sensitivity analysis: propensity calibration to adjust for migraine type, severity, and medication beliefs

	β	95% Confidence Interval	Percent Change[3] from Main PS-adjusted to PSC-adjusted models
Emotionality, Activity, and Shyness Questionnaire (EAS)			
EAS Sociability			
PS-adjusted (MoBa study only)[1]	0.02	-0.10 to 0.14	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	0.01	-0.13 to 0.14	-50.0%
EAS Emotionality			
PS-adjusted (MoBa study only)[1]	-0.01	-0.14 to 0.12	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	-0.01	-0.13 to 0.11	0.0%
EAS Activity			
PS-adjusted (MoBa study only)[1]	0.04	-0.08 to 0.17	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	0.03	-0.11 to 0.17	-25.0%
EAS Shyness			
PS-adjusted (MoBa study only)[1]	0.06	-0.07 to 0.19	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	0.04	-0.06 to 0.18	-33.3%
Ages and Stages Questionnaire (ASQ)	OR	95% Confidence Interval	Percent Change[3] from Main PS-adjusted to PSC-adjusted models
ASQ Gross Motor Delay			
PS-adjusted (MoBa study only)[1]	0.43	0.15 to 1.22	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	0.45	0.14 to 1.42	-4.7%
ASQ Fine Motor Delay			
PS-adjusted (MoBa study only)[1]	1.28	0.96 to 1.71	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	1.25	0.89 to 1.74	-2.4%
ASQ Communication Delay			
PS-adjusted (MoBa study only)[1]	1.02	0.42 to 2.48	
PSC-adjusted (MoBa and Internet Migraine studies)[2]	0.93	0.31 to 2.81	9.7%

1. Adjusted for the propensity for taking triptans during pregnancy, conditional on maternal age, pre-pregnancy BMI, reproductive history, marital status, maternal education, smoking or alcohol use during pregnancy, presence of depressive symptoms, pre-pregnancy triptan use, and co-medication use during pregnancy (acetaminophen, opioids, NSAIDs, antidepressants). PS-adjusted estimates are not IPC-weighted, and so differ slightly from those reported in Table 4.
2. Adjusted for the propensity for taking triptans during pregnancy (estimate from Table 2.3) and calibrated for migraine severity, migraine type, and attitude towards medication (BMQ Necessity and Concern scores), **not including** BMI and antidepressant exposure [inclusion of BMI and antidepressant use in PS did not result in substantial change in β estimates]
3. Percent change calculated as $[(PSC_{adjusted} – PS_{adjusted}) / PSC_{adjusted}] *100$

Figure 3.1. Inclusion and exclusion criteria for MoBa Study



CHAPTER IV
CHANGES IN NEURODEVELOPMENTAL OUTCOMES BETWEEN 18 AND 36 MONTHS IN CHILDREN WITH PRENATAL TRIPTAN EXPOSURE

Title: Changes in Neurodevelopmental Outcomes Between 18 and 36 Months in Children with Prenatal Triptan Exposure

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IV.0 ABSTRACT

Background. Triptans, a class of serotonin agonists, are the most commonly used acute antimigraine agent; they readily cross both the placenta and blood-brain barrier, and are plausible neurodevelopmental teratogens. Studies investigating the association between prenatal triptan exposure and neurodevelopment in children are sparse.

Methods. Using data from the Norwegian Mother and Child Cohort Study, a prospective birth cohort that includes nearly 40% of all pregnancies in Norway from 1999-2008, we identified 50,469 mother-child dyads who met inclusion criteria and were present for at least one follow-up assessment at 18 or 36 months post-partum. Neurodevelopment was assessed using the Child Behavior Checklist, the Emotionality, Activity, and Shyness Questionnaire, and the Ages and Stages Questionnaire. We used generalized estimating equations to evaluate change from 18 to 36 months for children prenatally exposed to triptans, relative to contrast groups.

Results. Among eligible participants (n=50,469), 1.0% used a triptan during pregnancy, 2.0% used triptans prior to pregnancy only, 8.0% reported migraine without triptan use, and 89.0% had no history of migraine. Children with prenatal triptan exposure had greater increases in emotionality (r-RR 2.18, 95%CI 1.03 to 4.53) and activity problems (r-RR 1.70, 95%CI 1.02 to 2.8) compared to children born to mothers who discontinued triptan use prior to pregnancy.

Conclusion. Prenatal triptan exposure was associated with emotional and behavioral dysregulation.

IV.1. Introduction.

Migraine is a chronic pain condition that affects approximately 20% of women of reproductive age.[5,6] Treatment options for migraine are primarily pharmacologic, and include both preventive medications as well analgesic medications, which are taken in response to an oncoming migraine episode. Among the analgesic medications, triptans, a class of serotonin 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor agonists that act on smooth muscle as well as the trigeminal cervical complex, are the most common prescription acute migraine medication.[9] To date, 10 studies have examined the safety of triptan use during pregnancy, but most have focused on pregnancy and very early life outcomes; triptans have been associated with pre-eclampsia, preterm birth, and increased risk of folate-deficient anemia, but not with major congenital malformations.[12,15,37,76] A recent meta-analysis found no increased risk of preterm birth or congenital malformation associated with prenatal triptan exposure, but did note an increased risk of spontaneous abortion;[14] an additional review of migraine treatment during pregnancy recommends that triptans may be used conservatively in pregnancy, if adequate pain relief is not achieved through acetaminophen alone.[15]

Studies of the effect of prenatal triptan on childhood neurodevelopment have been sparse, and results have been varied. Our previous work has shown that prenatal exposure to triptans, particularly in the first trimester, was associated with an increased risk of clinically-significant externalizing behavior in three year old children,[77] and additional work found no associations with motor

skills, communication, or temperament, after adjustment for migraine severity.[95] While examination of behavior at a single age is informative, understanding trajectories gives a more complete picture of child neurodevelopment. Understanding whether groups with prenatal triptan exposure were indistinguishable in early childhood but diverge as they progress in age, or conversely, had wide differences in early life but converge as they age, may yield important insights into the mechanism by which triptans affect the developing brain.

This study aims to quantify the effect of triptan use during pregnancy on the differences in neurodevelopment outcomes from 18 to 36 months between children. Among neurodevelopmental outcomes associated with triptan use during pregnancy, we also sought to determine whether timing of triptan exposure (first trimester, second/third trimester) is related to differences in change over time.

IV.2. Methods.

Norwegian Mother and Child Cohort Study (MoBa)

Between 1999 and 2008, the Norwegian Institute of Public Health invited women to participate in the Norwegian Mother and Child Cohort Study (MoBa).[47] Women were invited prior to their first routine ultrasound appointment (gestational week 13-17). A total of 108,841 women consented to participate (participation rate 42.7%), with 84.8% of the participants completing the six month post-partum questionnaire and 60.2% completing the 36 month post-

partum questionnaire.[46,78] Written informed consent was obtained from all participants, and the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study; this analysis was granted an exemption from the University of Massachusetts Medical School Institutional Review Board. Data were taken from the quality-ensured Data Version 6, released by MoBa in 2012 and includes all children born before 2009 for whom the age three years questionnaire was received by May 4, 2011; these data were linked to the Medical Birth Registry of Norway (MBRN) using participants' 11-digit personal identification numbers.

Exclusion criteria were: infant not born alive, multiple births, major congenital malformations or chromosomal abnormalities, and indication of triptan exposure where we were unable to determine whether the triptan was taken prior to or during pregnancy. In total, 7,220 women were excluded. We included 59,468 mother-child dyads with complete outcome data at the 18 and/or 36-month follow up. We conducted a complete-case analysis in which dyads with missing data on variables thought to be confounders were excluded, leaving an analytic sample of 50,469 women, of which 14,790 had complete outcome data at 18 month follow-up only, 6,774 had complete data only at 36 months, and 28,905 had complete outcome data at both 18 and 36 months. In analyses of timing of triptan exposure, we included only 5,484 women with a self-reported history of migraine headache at the first pregnancy questionnaire. Flow through the study is further characterized in Figure 4.1.

Triptan Exposure

Information on exposure to medications was gathered prospectively from two prenatal (Q1-gestational week17, Q3-gestational week 30) and one postpartum questionnaire (Q4-6 months post partum). Women were asked to indicate when they had taken a medication (during the six months before pregnancy, during weeks 0-4, 5-8, 9-12, and/or 13 or later for Q1, during weeks 13-16, 17-20, 21-24, 25-28, and/or week 29 or later for Q3, and from week 30 until birth for Q4), and to write the name of the medication in a text box. Women who included multiple medications in a single text box (e.g., naratriptan and acetaminophen) were assumed to have been exposed to all listed medications in all time periods. Medications were classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System.[48] The ATC code N02CC was used to determine triptan exposure. Triptan medications were further classified into specific compounds: N02CC01 (sumatriptan), N02CC02 (naratriptan), N02CC03 (zolmitriptan), N02CC04 (rizatriptan), N02CC05 (almotriptan), N02CC06 (eletriptan), and N02CC07 (frovatriptan). No information was available on formulation (tablet vs. injection or nasal spray) or dose.

Information on migraine was gathered prospectively from pregnancy questionnaire 1, which asked whether the woman had migraine within 6 months prior to pregnancy or during pregnancy, up to the time of filling out the questionnaire (approximately week 17 of pregnancy). Four different exposure

groups were created based on information about triptan use and migraine before and during pregnancy: prenatal triptan exposure, pre-pregnancy triptan use, migraine only, and population comparison. It is possible that some women who developed migraine later in pregnancy would be incorrectly classified as not having migraine: pregnancy questionnaire 3 asks jointly about "migraine/headache" rather than specifically about migraine. First onset of migraine in pregnancy is rare, and most often occurs in the first trimester,[96] and so we would expect the number of misclassified women to be low.

Neurodevelopmental Outcomes

Child Behavior Checklist (CBCL)

The Child Behavior Checklist (CBCL) is a validated measure of child behavior widely used in both clinical and research practice; a shortened version, which has been validated in a Norwegian population, was used in MoBa.[52] The externalizing (including the "attention problems" and aggressive behavior" subscales) and internalizing (including the "emotionally reactive," "anxious/depressed," and "somatic complaints" subscales) domains were used. Standardized z-scores were computed for the study sample; higher z-scores indicate more problems within a given domain. We classified scores as being clinically meaningful (z-score ≥ 1.50, indicating behaviors more extreme than 94% of the sample).

Emotionality Activity and Shyness Temperament Questionnaire (EAS)

The Emotionality, Activity, and Shyness Temperament Questionnaire measures four temperament domains (emotionality, shyness, sociability, and activity). A substantial body of literature has linked early childhood temperament to later life depression and other psychiatric diagnoses.[79,80] The shortened version of the EAS used in the MoBa study, was developed with Norwegian social norms in mind, and includes 12 descriptions (e.g. “Your child likes to be with people;” “Your child cries easily.”), and parents are asked to rate how well each statement applies to their child; in a Norwegian sample, the four factor structure of the original scale was reproduced, and internal consistency within each scale ranged from α=0.48 to α=0.79.[81] We calculated z-scores based on the sample distribution of each domain. Higher z-scores indicate greater parental endorsement of each temperament trait (e.g. more shy, or more sociable) relative to parental reports of other children in the sample. We additionally classified scores to indicate temperamental traits more extreme than 94% of the sample (z-score ≥ 1.50).

Ages and Stages Questionnaire (ASQ)

The Ages and Stages Questionnaire is a parent-completed questionnaire appropriate for children aged four months to five years. Deficits detected by the ASQ have been shown to be predictive of school difficulties in older children,[82] and fine motor skills are highly predictive of later academic achievement.[83] The abbreviated ASQ used in MoBa includes questions about developmental milestone attainment in three major categories: gross motor, fine motor, and

communication; this shortened version has been validated in a Norwegian population, and had excellent test-retest reliability (94%) and agreement between parents and professional examiners, as well as acceptable sensitivity and specificity (72% and 86%, respectively)[84]. Scores on the ASQ domains were highly skewed; to address this, we categorized children at each time point as having problems in a given domain if they scored at or above the 94th percentile in the sample, versus scoring below the 98th percentile. This categorization is comparable to using a z-score of $\geq$1.5 as a cutoff.

Concomitant medication use

We examined other pain medications and psychotropic medications as potential confounders, using the following ATC codes: N02BE01 (acetaminophen), N02A (opioids), M01A (non-steroidal anti-inflammatory drugs, NSAIDs), N06A (antidepressants), N05CD02, N05CD03, N05CD08, N05BA01, N05BA05, N05BA12 (benzodiazepines), and N03A (anti-epileptics). All co-medications were categorized as ever vs. never used in pregnancy and prior to pregnancy.

Maternal Characteristics

Maternal age, pre-pregnancy body mass index (BMI) (underweight or <18.5 kg/m2, normal weight or 18.5-25 kg/m2, or overweight, >25 kg/m2 according to WHO guidelines), education (primary or secondary vs university or higher), marital status (married or cohabiting vs other), parity (multiparous vs. primiparous) and depression history (yes or no) were all ascertained by self-

report on Q1. Smoking (ever during pregnancy vs. not during pregnancy) and alcohol use (ever during pregnancy vs. not during pregnancy) were ascertained by combining information from self-report as well as linkage to the Medical Birth Registry of Norway.

Loss to follow-up

We observed substantial attrition at the 18 and 36-month follow-up questionnaires. To adjust for the potential for selection bias due to attrition, we constructed stabilized inverse probability of treatment weights (IPCW). The method for creating IPCW is described in great detail elsewhere;[62] briefly, the numerator of the stabilized weight is equal to the predicted probability of attrition in the sample, and the denominator of the weight is equal to the predicted probability of attrition, conditional on measured confounders. In our study, maternal age, pre-pregnancy BMI, marital status, reproductive history, migraine history, and use of triptans prior to and during pregnancy were included in the IPCW. We created IPCW via logistic regression for dropout at 18 and 36 months separately, then combined the weights to create a total weight used in further analysis. This method reduces the impact of selection bias on effect estimates by ensuring balance of measured predictors of dropout within strata of exposure.

Statistical Analysis

The purpose of this analysis was to examine differences in neurodevelopmental changes over time that were associated with prenatal triptan exposure. Our analysis proceeded in several steps. First, we examined

descriptive statistics across the four main exposure groups and compared absolute percentages (for categorical measures); we considered a difference greater than 5% to be meaningful. Next, we used generalized estimating equations (GEE) to fit generalized linear models, specifying a binomial distribution and a log link, that included fixed effects for exposure group (prenatal triptan exposure, pre-pregnancy triptan use, migraine only, and population comparison), time (18 and 36 months), and their interaction. GEE models were selected for their approach to missing outcome data (using all available observations, rather than case wise deletion for observations present only at a single time point), as well as their ability to model covariation using flexible covariance structures among repeated measures. Based on comparisons between the empirical and model-based covariance matrices, we selected an exchangeable covariance structure for all models. The resulting estimates represent the change in risk (r-RR) of having a clinically-meaningful neurodevelopmental outcome between 18 and 36 months of age for children with prenatal triptan exposure, relative to each contrast group (pre-pregnancy triptan use only, migraine only, and population comparison), with 95% confidence intervals (CI) calculated using robust standard errors. Models were adjusted for maternal characteristics (age, pre-pregnancy BMI, parity, marital status, education, smoking or alcohol use in pregnancy, depression symptom severity) and concomitant medication use (NSAIDs, acetaminophen, opioids, antidepressants). To assist in the interpretation of the data, we used model-

based predicted probability of outcome at 18 and 36 months to create line graphs of the change in outcome over time for each exposure group. Examination of graphs were useful because an r-RR greater than 1 could be a result of qualitatively different phenomena (e.g. greater increased risk over time in triptan group relative to increased risks observed in the contrast group, increased risk in the triptan users group and decreased risk in the comparison group, etc.).

Second, for the neurodevelopmental outcomes which appeared to be associated with any triptan use during pregnancy, we developed marginal structural models (MSM) to understand the effect of exposure timing on the difference in change of the outcome from 18 to 36 months. We fit marginal structural models (MSM) with stabilized inverse probability of treatment weights (IPTW) to adjust for measured confounding by baseline characteristics (maternal age, pre-pregnancy BMI, sociodemographic variables), time-invariant predictors (smoking and alcohol use during pregnancy, folate supplementation, maternal depression severity) as well as time-varying confounders (other medication use, including acetaminophen, NSAIDs, opioids, and antidepressants). The MSM approach results in unbiased effect estimates under assumptions of exchangeability and positivity, and allows for appropriate adjustment for the effects of confounders that are also mediators.[59,97] We created the IPTW via logistic regression at each exposure time point (pre-pregnancy, first trimester, second/third trimester) created an IPTW equal to the product of the weight from each time point. The product of the IPTW and IPCW was used as the total MSM

weight, to account for both measured confounding and loss to follow-up. Weights were examined for extreme values. After identifying a small number of extreme weights (>32) in women who had no history of triptan use prior to second/third trimester initiation, we elected to truncate weights at the 99th percentile. Weighted GEE models were then fit within the migraine-only group. Results are given as the change in risk ratio over time (r-RR) for triptan exposure at each time point (pre-pregnancy, first trimester, second/third trimester) relative to no exposure during that time, with 95% confidence intervals estimated using robust standard errors to account for clustering induced by weighting.

For analyses conducted in the first and second steps, we interpreted a significant time-by-group interaction (95% confidence interval that did not include 1) to be indicative of a difference in change between exposure groups, from 18 to 36 months of follow-up.

IV.3. Results.

After applying study inclusion and exclusion criteria, 50,469 women were included, of whom 1.0% reported using a triptan at least once during pregnancy, 2.0% used triptans prior to pregnancy only, and 8.0% had a history of migraine with no use of triptans. Among the 5,484 women with history of migraine (10.9% of the total sample), 27.1% used triptans prior to pregnancy, 6.9% reported use during the first trimester, and 3.1% reported use during the second or third trimester.

Women who reported triptan use during pregnancy differed little from comparison groups in demographic characteristics: age, pre-pregnancy BMI, parity, educational attainment, smoking during pregnancy, and folate supplementation were similar across groups. However, women who used triptan during pregnancy had higher mean depression and anxiety symptom scores than women who discontinued triptan use (0.16 vs. 0.03). In addition, women with triptan use during pregnancy were more likely to use other medications at higher rates during pregnancy compared to women who discontinued triptan use, including opioids (13.3% vs. 4.6%), acetaminophen (78.2% vs. 69.8%), and NSAIDs (22.0% vs. 10.1%). Further characteristics of the study sample are described in Table 4.1.

The Externalizing Behaviors subscale of the CBCL, as well as the Emotionality and Activity subscales of the EAS, describe a set of behaviors characterized by increased activity, aggression, and emotional reactivity. Children whose mothers used triptans during pregnancy had substantial increased risk of high emotionality, compared to static or decreased emotionality in children whose mothers used triptans only prior to pregnancy (r-RR 2.18, 95%CI 1.03 to 4.53) as well as those with a history of migraine without triptan use (r-RR 2.51, 95%CI 1.27 to 4.90) and a migraine-free population comparison group (r-RR 2.16, 95%CI 1.14 to 2.14) (Table 4.2, Figure 4.2). When we examined the association between timing of triptan exposure within the group of women with migraine using marginal structural models (MSM) with inverse

probability weights (IPW), the r-RR estimate for first trimester exposure relative to no first trimester exposure was 1.54 (95%CI 0.57 to 4.13) and the r-RR estimate for second/third trimester exposure relative to no second/third trimester exposure was 2.41 (95%CI 0.71 to 8.20) (Table 4.3). We also observed differences in rate of change for activity: children with prenatal triptan exposure had lesser decreases in activity from 18 to 36 months, relative to the pre-pregnancy (r-RR 1.70, 95%CI 1.02 to 2.80), migraine-only (r-RR 1.57, 95%CI 1.04 to 2.36), and population comparison (r-RR 1.67, 95%CI 1.14 to 2.14) groups (Table 4.2). Examining the association between timing of exposure, the r-RR estimate for first trimester exposure relative to no first trimester exposure was 1.98 (95%CI 0.90 to 4.34) and the r-RR estimate for second/third trimester exposure relative to no second/third trimester exposure was 1.37 (95%CI 0.46 to 4.10) (Table 4.3). Externalizing behavior in children with prenatal triptan exposure, as measured by the CBCL, remained elevated compared to all contrast groups, but did not show evidence of increase or decrease over time (Table 4.2, Figure 4.2).

The Internalizing Behavior subscale of the CBCL, along with the Shyness and Sociability subscales of the EAS, describe a set of symptoms characterized by anxiety, shyness, and withdrawal. Change in shyness and sociability were not associated with use of triptans during pregnancy (Table 4.2, Figure 4.3). We saw no differences in change of risk for gross motor, fine motor, or communication problems from 18 to 36 months for children with prenatal triptan exposure, relative to any comparison group (Table 4.2, Figure 4.3).

IV.4. Discussion.

We observed several neurodevelopmental domains in which change in neurodevelopment was substantially different for children with prenatal triptan exposure, including emotionality and activity; these domains appear to be associated with prenatal triptan exposure specifically, rather than migraine alone. There were no overall differences in internalizing behaviors and shyness and motor problems or communication problems associated with either triptan exposure or migraine.

Our previous work, which was the first to report on neurodevelopmental sequelae of prenatal triptan exposure, indicated that exposed children had higher rates of externalizing problems at 36 months than those without prenatal exposure.[77] The findings from the current study suggest that these elevated rates of externalizing behavior remain relatively stable between 18 and 36 months; additionally, the observed increases in emotionality and activity describe a consistent profile of temperamental and behavioral dysregulation associated with prenatal triptan exposure.

A possible alternative explanation for our findings is that the triptan group identified in our study should be thought of as proxies for migraine severity, with the women who used triptans in pregnancy having the most severe migraine, women who discontinued triptan use prior to pregnancy as having less severe illness, and women with migraine who did not use triptans as being the least

severe. If this were the case, we might expect to see the prenatal exposure and pre-pregnancy only comparison group showing the smallest effect size, followed by increasing effect magnitude for contrasts with the migraine-only and population comparison groups. However, our results showed relatively stable effect sizes for prenatal triptan exposure compared to all contrast groups. Overall, our results suggest a distinct profile for children with prenatal exposure to triptans in which changes in externalizing-type behaviors from 18 to 36 months were markedly different from all comparison groups..

Misclassification of triptan exposure may also explain our findings. Maternal report of analgesic medication use in pregnancy has been shown to have low sensitivity but high specificity,[50] suggesting that while reported medication use in pregnancy is likely to be accurate, some women have been inaccurately classified as unexposed. The MoBa study collects exposure data prospectively, and so exposure misclassification is likely to be nondifferential; however, if maternal anxiety is associated with differences in reporting of medication exposure, it is possible that misclassification of exposure, with its associated unpredictable biases, could be driving the effect estimates for prenatal triptan exposure. Similarly, it is possible that women classified as pre-pregnancy triptan users were in fact early first trimester users instead. If this misclassification is non-differential, it could also be a source of bias.

The prevalence of externalizing problems among children with prenatal triptan exposure were elevated at 18 months and remained relatively stable at 36

months, while prevalence of emotionality and activity both increased from 18 to 36 months in children with prenatal exposure, compared to all contrast groups. Emotionality, in the context of the Emotionality, Activity, and Shyness Questionnaire includes items that tap emotional reactivity, while items in the Activity subscale ask about higher levels of physical activity. Of potential interest is that fact that the emotionality and activity domains, as well as the externalizing behavior domain, ask parents to report on observable behaviors in their children, such as temper explosions, hyperactivity, and coordination problems, while the sociability and shyness domains, as well as internalizing behaviors, ask parents to report on their child's internal state. Parents are better reporters of externalizing symptoms while children are better reporters of internalizing symptoms.[98] Future studies should include replicating these findings in an older cohort of children, in which child self-report of psychological or behavioral problems is available.

The results of this study have important clinical implications for prescribers treating women with migraine during pregnancy. A recent review of migraine treatment during pregnancy has recommended that triptans may be used conservatively during pregnancy, if other therapies such as acetaminophen do not provide adequate pain relief;[15] in addition, a recent meta-analysis of triptan use in pregnancy found that prenatal triptan use was associated with an increased risk of spontaneous abortion, although not of preterm birth or congenital malformations.[14] The current study expands the potentially-negative

outcomes that may result from prenatal triptan use, and providers who treat pregnant women with migraine should consider the risks accordingly. There are also implications for clinicians who may see children born to mothers with migraine headache. Numerous studies have shown that early childhood emotional and behavioral problems are predictive of academic and emotional difficulties in adolescence,[29,39,51,99] but that early intervention can effectively reduce these problems.[100,101] Children whose mothers have a history of migraine, and particularly those whose mothers took triptans during pregnancy, may benefit from additional monitoring and potentially, treatment.

There are several important limitations to consider when evaluating the findings from this study. First, MoBa does not collect information on migraine severity. Our previous work has shown that women with more severe migraine are more likely to take triptans during pregnancy,[95] although subsequent adjustment for migraine severity resulted in modest changes in effect estimates. Confounding by indication is difficult to control,[26] and cannot be ruled out as an alternative explanation for the observed results. Second, no information was available on triptan formulation or dose; additionally, we had insufficient power to analyze specific triptans. Triptans have different pharmacokinetic properties and differing affinities for subclasses of serotonin receptors,[102] and considering these medications as a class, without consideration for dose or formulation, may elide important information on risks specific to individual compounds.

These limitations are balanced by important strengths: first, we used advanced analytic methods to appropriately adjust for time-varying confounding by concomitant medication use. Triptan exposure changes over time, and women who use triptans in pregnancy also use many other medications, several of which have previously been associated with neurodevelopmental problems in children.[30,31,103] Failure to appropriately adjust for these medications may result in incorrectly attributing effects to triptan exposure that are in fact due to other medications. Our study was set in a large, prospective birth cohort with data available on both over the counter and prescription medication use, allowing for careful consideration of concomitant medication use, as well as other important confounders such as severity of maternal depressive and anxiety symptoms.

Taken together, the findings from this study suggest that fetal exposure to triptans is associated with a set of traits related to emotional and behavioral dysregulation. In light of this and other recent studies, we recommend caution in the use of triptan medications during pregnancy, until future research clarifies the role of the underlying migraine.

Table 4.1. Maternal and pregnancy characteristics

	Migraine			No Migraine
	Triptans in pregnancy	Triptans prior to pregnancy	No triptan history	Population Comparison
	N=495	N=1,002	N=4,050	N=44,922
Age in years (Mean, SD)	30.9(4.3)	30.4(4.1)	30.2(4.5)	30.3(4.4)
Body Mass Index (kg/m^2)				
<18.5	12(2.4)	25(2.5)	145(3.6)	1,216(2.7)
18.5-25	307(62.0)	608(60.7)	2,491(61.5)	29,747(66.2)
>25	176(35.6)	369(36.8)	1,414(34.9)	13,959(31.1)
Multiparous	254(51.3)	467(46.6)	2,204(54.4)	24,467(54.5)
Married or cohabitating	474(95.8)	980(97.8)	3,922(96.8)	43,761(97.4)
Mother Education				
Primary or secondary	165(33.3)	339(33.8)	1,533(37.9)	14,511(32.3)
University or higher	330(66.7)	663(66.2)	2,517(62.2)	30,411(67.7)
Smoking during pregnancy	57(11.5)	118(11.8)	552(13.6)	5,236(11.7)
Alcohol during pregnancy	95(19.2)	146(14.6)	623(15.4)	7,506(16.7)
Folate Supplementation	299(60.4)	618(61.7)	2,359(58.3)	26,462(58.9)
Multivitamin Supplementation	186(37.6)	426(42.5)	1,610(39.8)	16,661(37.1)
Migraine Preventive Therapy	8(1.6)	21(2.1)	22(0.5)	0(0.0)
Opioids				
Pre-pregnancy	40(8.1)	52(5.2)	208(5.1)	609(1.4)
In pregnancy	66(13.3)	46(4.6)	188(4.6)	631(1.4)
Paracetamol/acetaminophen				
Pre-pregnancy	233(47.1)	475(47.4)	1,794(44.3)	11,474(25.5)
In pregnancy	387(78.2)	699(69.8)	2,596(34.1)	19,331(43.0)
NSAIDs				
Pre-pregnancy	109(22.0)	247(24.7)	938(23.1)	4,450(9.9)
In pregnancy	109(22.0)	101(10.1)	509(12.6)	2,652(5.9)
Antidepressants				
Pre-pregnancy	24(4.9)	48(4.8)	158(3.9)	1,042(2.3)
In pregnancy	11(2.2)	11(1.1)	67(1.7)	426(1.0)
Anti-convulsants				
Pre-pregnancy	2(0.4)	7(0.7)	10(0.3)	41(0.1)
In pregnancy	1(0.2)	3(0.3)	13(0.3)	86(0.2)
Benzodiazepines				
Pre-pregnancy	8(1.6)	13(1.3)	38(0.9)	240(0.5)
In pregnancy	8(1.6)	5(0.5)	19(0.5)	165(0.4)
Maternal depressive/anxiety symptoms[1] (Mean, SD)	0.16(1.70)	0.03(1.84)	0.23(1.88)	-0.12(1.63)
Pre-eclampsia	33(6.7)	47(4.7)	170(4.2)	1,536(3.4)
Small for Gestational Age	35(7.1)	65(6.5)	269(6.6)	2,737(6.1)
Apgar 5 (<7)	7(1.4)	9(0.9)	30(0.7)	415(0.9)
Preterm	19(3.8)	45(4.5)	193(4.8)	2,026(4.5)
Low Birth Weight	11(2.2)	24(2.4)	108(2.7)	1047(2.3)

1. Average z-score from the Symptom Checklist (SCL); higher positive scores indicate more depressive symptoms

Table 4.2. Change in neurodevelopmental outcome from 18 to 36 months: change over time for prenatal triptan exposure, relative to pre-pregnancy triptan use, migraine-only, and population comparison

	Percent$_{18m}$[1]	Percent $_{36m}$	Unadjusted rRR[2]	Unadjusted 95% Confidence Interval	Multivariable Adjusted[3] rRR	Multivariable Adjusted[3] 95% Confidence Interval
CBCL Externalizing Behavior						
Prenatal Triptan Use	11.0	10.0				
Vs. Pre-pregnancy triptans only	7.8	6.5	1.11	0.70 to 1.73	1.11	0.70 to 1.75
Vs. Migraine only	8.1	7.6	0.99	0.69 to 1.43	1.00	0.70 to 1.43
Vs. Population comparison	7.7	6.5	1.11	0.79 to 1.54	1.11	0.79 to 1.54
EAS Emotionality						
Prenatal Triptan Use	3.2	6.3				
Vs. Pre-pregnancy triptans only	5.3	4.7	2.18	1.03 to 4.57	2.18	1.03 to 4.53
Vs. Migraine only	5.1	3.9	2.51	1.28 to 4.90	2.51	1.27 to 4.90
Vs. Population comparison	5.2	4.7	2.18	1.14 to 4.10	2.16	1.14 to 4.10
EAS Activity						
Prenatal Triptan Use	9.2	8.3				
Vs. Pre-pregnancy triptans only	9.7	4.7	1.68	1.02 to 2.80	1.70	1.02 to 2.80
Vs. Migraine only	9.8	5.3	1.57	1.05 to 2.34	1.57	1.04 to 2.36
Vs. Population comparison	9.8	5.1	1.67	1.14 to 2.41	1.67	1.14 to 2.42
CBCL Internalizing Behavior						
Prenatal Triptan Use	8.1	9.5				
Vs. Pre-pregnancy triptans only	6.2	10.8	0.70	0.41 to 1.16	0.69	0.41 to 1.14
Vs. Migraine only	8.7	10.5	1.01	0.66 to 1.57	1.02	0.66 to 1.57
Vs. Population comparison	7.5	8.1	1.14	0.75 to 1.72	1.12	0.74 to 1.70
EAS Shyness						
Prenatal Triptan Use	4.9	12.3				
Vs. Pre-pregnancy triptans only	3.5	9.6	0.93	0.53 to 1.65	0.92	0.52 to 1.63
Vs. Migraine only	4.0	7.7	1.30	0.81 to 2.08	1.30	0.81 to 2.08
Vs. Population comparison	4.5	8.1	1.40	0.91 to 2.16	1.40	0.91 to 2.16
EAS Sociability						
Prenatal Triptan Use	8.8	6.3				
Vs. Pre-pregnancy triptans only	6.8	6.4	0.77	0.45 to 1.38	0.78	0.44 to 1.38
Vs. Migraine only	9.3	6.1	1.12	0.69 to 1.80	1.13	0.70 to 1.82
Vs. Population comparison	8.0	5.7	1.02	0.65 to 1.62	1.03	0.65 to 1.63

1. Percent is the percent with outcome, respectively, at each measurement (18 and 36 months post-partum)
2. rRR(ratio of risk ratios) is the group-by-time interaction coefficient from the generalized estimating equation model; it is the difference in change from 18 to 36 months for prenatal triptan exposure, relative to each contrast group
3. Models are adjusted for maternal age, pre-pregnancy body mass index, parity, marital status, education, smoking or alcohol use during pregnancy, Symptom Checklist depression/anxiety severity score, and concomitant medication use during pregnancy (acetaminophen, opioids, NSAIDs, antidepressants).

Table 4.2. (continued)

	Percent$_{18m}$[1]	Percent $_{36m}$	Unadjusted rRR[2]	Unadjusted 95% Confidence Interval	Multivariable Adjusted[3] rRR	Multivariable Adjusted[3] 95% Confidence Interval
ASQ Gross Motor						
Prenatal Triptan Use	1.6	1.2				
Vs. Pre-pregnancy triptans only	3.3	3.0	0.86	0.23 to 3.20	0.86	0.23 to 3.19
Vs. Migraine only	2.3	3.0	0.58	0.16 to 2.02	0.58	0.17 to 2.03
Vs. Population comparison	2.3	3.1	0.55	0.16 to 1.87	0.55	0.16 to 1.88
ASQ Fine Motor						
Prenatal Triptan Use	13.9	9.5				
Vs. Pre-pregnancy triptans only	11.6	9.4	0.84	0.52 to 1.36	0.85	0.52 to 1.37
Vs. Migraine only	11.5	9.2	0.85	0.56 to 1.28	0.85	0.56 to 1.29
Vs. Population comparison	11.8	10.4	0.78	0.52 to 1.13	0.77	0.52 to 1.14
ASQ Communication						
Prenatal Triptan Use	3.4	4.6				
Vs. Pre-pregnancy triptans only	4.1	4.5	1.20	0.55 to 2.64	1.22	0.56 to 2.68
Vs. Migraine only	3.8	5.2	0.96	0.48 to 1.93	0.97	0.48 to 1.95
Vs. Population comparison	4.1	5.0	1.09	0.56 to 2.16	1.12	0.57 to 2.19

1. Percent is the percent with outcome, respectively, at each measurement (18 and 36 months post-partum)
2. rRR(ratio of risk ratios) is the group-by-time interaction coefficient from the generalized estimating equation model; it is the difference in change from 18 to 36 months for prenatal triptan exposure, relative to each contrast group.
3. Models are adjusted for maternal age, pre-pregnancy body mass index, parity, marital status, education, smoking or alcohol use during pregnancy, Symptom Checklist depression/anxiety severity score, and concomitant medication use during pregnancy (acetaminophen, opioids, NSAIDs, antidepressants

Table 4.3. Change in neurodevelopmental outcome from 18 to 36 months: change over time associated with timing of triptan exposure, within migraine-only sample (N=5,484)

	Percent$_{18m}$[1]	Percent $_{36m}$	Unadjusted rRR[2]	Unadjusted 95% Confidence Interval	MSM[3] rRR	MSM[3] 95% Confidence Interval
CBCL Externalizing Behavior						
Pre-pregnancy	8.4	7.5	0.94	0.67 to 1.30	0.90	0.64 to 1.25
First Trimester	11.6	11.1	1.16	0.73 to 1.86	1.01	0.56 to 1.80
Second/Third Trimester	10.7	9.8	0.96	0.48 to 1.91	0.50	0.17 to 1.48
EAS Emotionality						
Pre-pregnancy	4.7	4.7	1.07	0.69 to 1.67	1.07	0.68 to 1.67
First Trimester	3.8	5.6	1.43	0.58 to 3.51	1.54	0.57 to 4.13
Second/Third Trimester	4.0	7.1	1.52	0.48 to 4.85	2.41	0.71 to 8.20
EAS Activity						
Pre-pregnancy	9.6	5.7	0.90	0.63 to 1.28	0.88	0.61 to 1.28
First Trimester	9.3	8.9	1.56	0.90 to 2.71	1.98	0.90 to 4.34
Second/Third Trimester	9.4	10.7	1.56	0.76 to 3.21	1.37	0.46 to 4.10

1. Percent is the percent with outcome at each measurement (18 and 36 months post-partum), among those with exposure at each time point (e.g.: Percent with externalizing problems at 18 months with prenatal triptan use ={ [75 / 1002] *100 }= 7.49%; percent with gross motor problems at 36 months with first trimester triptan use ={ [56 / 270] *100 }= 20.74%. Windows of triptan exposure are not mutually exclusive).
2. rRR (ratio of risk ratios) is the group-by-time interaction coefficient from the generalized estimating equation model; it is the difference in change from 18 to 36 months for each group, relative to no exposure during that time point.
3. Models are weighted by the product of stabilized inverse probability of censoring weight (IPCW) and inverse probability of treatment weight (IPTW); IPCW is the probability of dropout, conditional on maternal age, pre-pregnancy BMI, marital status, parity, migraine history, use of triptans prior to and during pregnancy. IPTW includes baseline covariates (maternal age, pre-pregnancy BMI, sociodemographic variables), time-invariant predictors (smoking and alcohol use during pregnancy, folate supplementation, maternal depression severity), time-varying concomitant medication use (acetaminophen, NSAIDs, opioids, antidepressants), and treatment history (triptan use).

Figure 4.1. Inclusion and exclusion criteria and flow through study

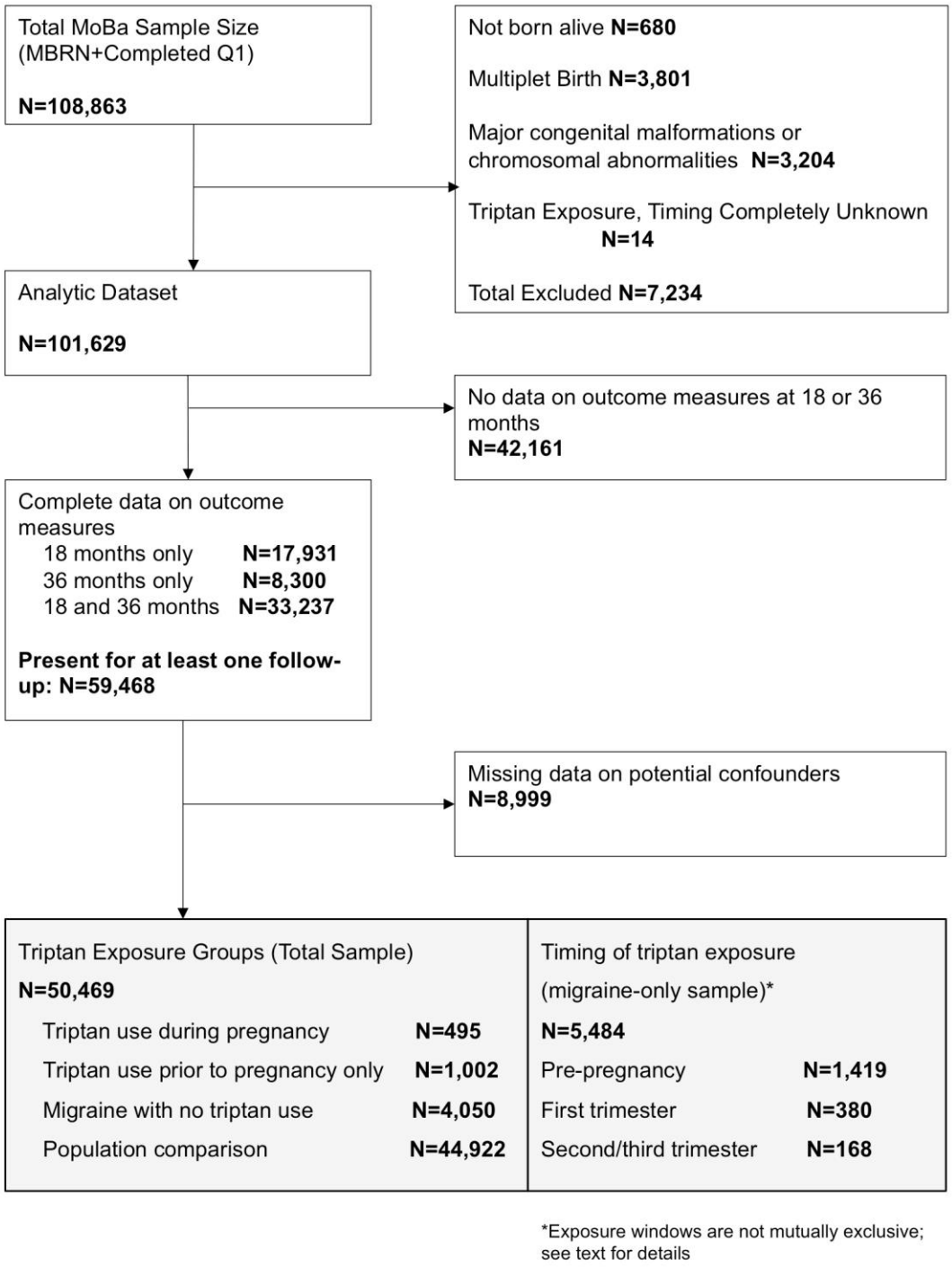


Figure 4.2. Changes in externalizing behavior, emotionality, and activity from 18 to 36 months

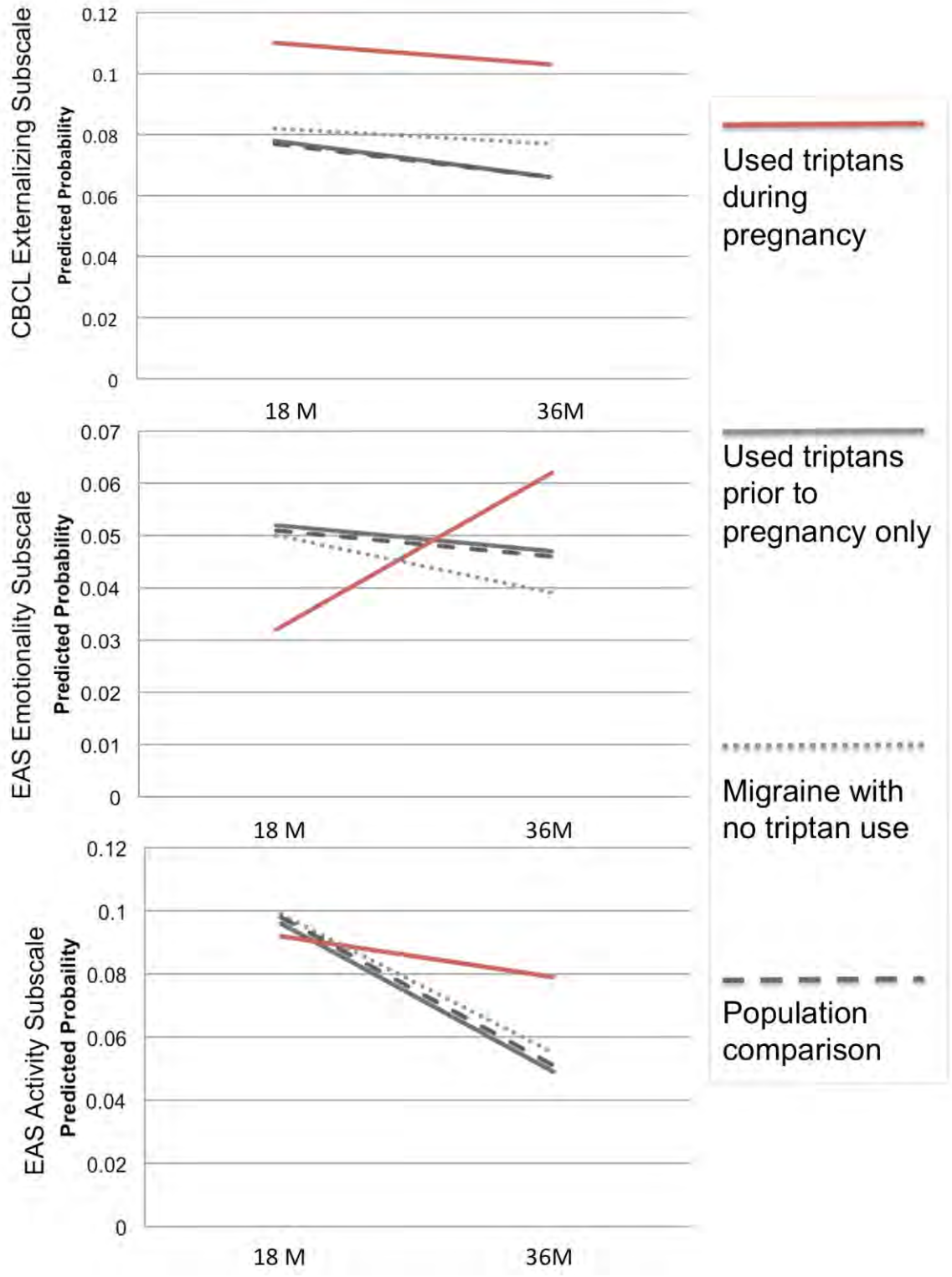


Figure 4.3. Changes in internalizing behavior, shyness, and sociability from 18 to 36 months

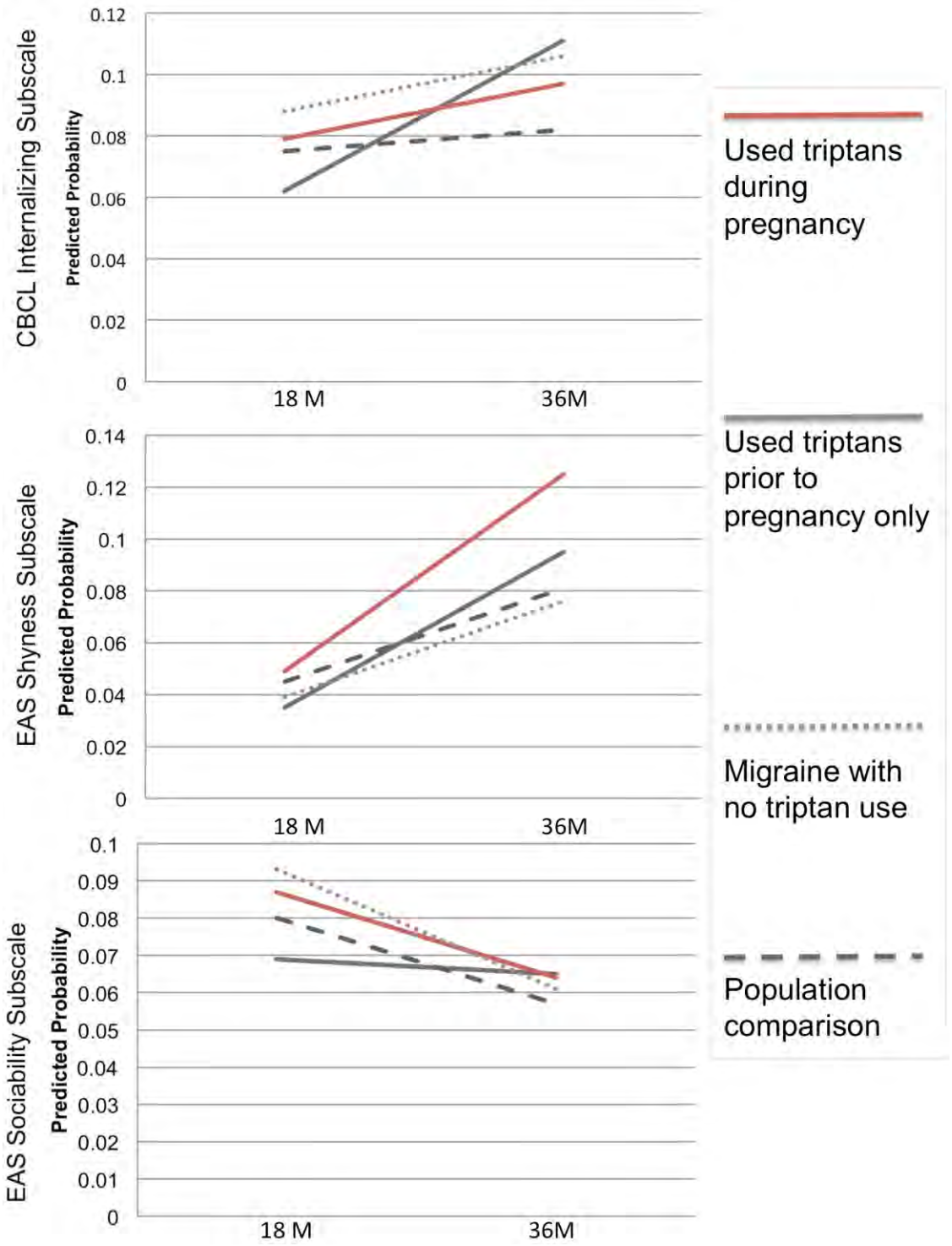
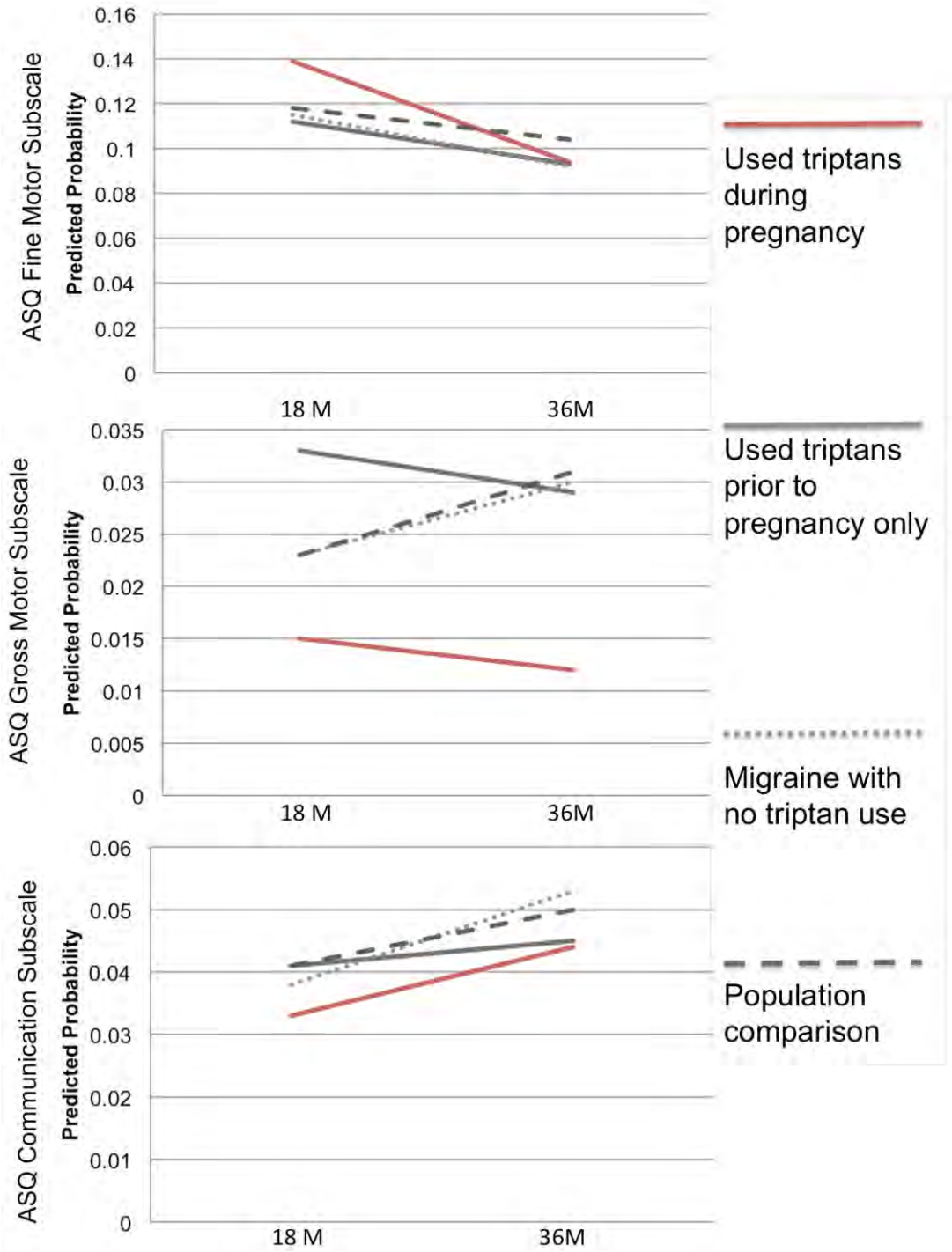


Figure 4.4. Changes in fine motor, gross motor, and communication from 18 to 36 months



CHAPTER V

DISCUSSION AND CONCLUSIONS

V.1. Summary of findings

This dissertation project set out to examine the association between prenatal exposure to triptan medications and a spectrum of neurodevelopmental outcomes in children, using causal inference methods in order to address methodological challenges that are specific to triptans. Triptan exposure during fetal development has been linked to several pregnancy and delivery outcomes,[14,15] but no previous studies have examined the association between prenatal triptan exposure and differences in neurodevelopment in children. Triptans are serotonin 1_B, 1_D, and 1_F receptor agonists, which are involved in fetal brain development, particularly for subcortical structures and projections from subcortical structures to neocortex.[18,19] We hypothesized that children exposed to triptans during fetal development would exhibit neurodevelopmental differences from children without prenatal triptan exposure.

In the first aim, we first compared the risk of internalizing and externalizing behaviors in children with prenatal triptan exposure to each of three comparison groups: children whose mothers discontinued triptan use prior to pregnancy, children whose mothers reported a history of migraine with no triptan use before or during pregnancy, and a population comparison group with no history of migraine or triptan use. We observed that at 36 months of age, children with prenatal triptan exposure had a substantially higher risk of clinically meaningful externalizing problems compared to all comparison groups, after adjustment for multiple potential confounders including maternal characteristics and concomitant

medication use; we observed no association between triptan exposure and internalizing symptoms. In order to determine whether these risks were specific to timing of exposure, we conducted further analyses using marginal structural models. These analyses yielded several important findings. First, the risk of externalizing behaviors was associated primarily with first trimester triptan exposure. Second, in examining timing of triptan exposure and internalizing symptoms, we found that in traditional multivariable adjusted models, pre-pregnancy exposure was associated with an increased risk of internalizing symptoms, but that use of marginal structural models, which correctly adjust for time-varying confounding using weighting methods, this risk was attenuated. These analyses were limited, however, by our inability to adjust for several potentially important confounders which were unmeasured in MoBa, including migraine type and severity, as well as maternal attitudes towards medication use.

In order to address the limitations of first study, in the second dissertation aim, we made use of an external validation study that contained information these important confounders, and used propensity score calibration to adjust our effect estimates. The outcomes included in the second study were: temperament characteristics (emotionality, activity, shyness, and sociability), psychomotor function, and communication skills. We found that migraine severity and maternal attitudes towards medication use were associated with triptan use during pregnancy, but that migraine type (with or without aura) was not. In this second study, prenatal triptan use was not associated with differences in temperament,

psychomotor function, or communication skills; however, even within the context of an essentially null study, propensity score calibration resulted in a reduction in bias of effect estimates of between 5—50%, suggesting that migraine severity and maternal attitudes towards medication use play an important role in the association between prenatal triptan exposure and neurodevelopment.

Recognizing that neurodevelopment is by definition a dynamic process, in the third aim, we examined changes in neurodevelopmental outcomes between 18 and 36 months of age in children with prenatal triptan exposure compared to children whose mothers discontinued triptan use prior to pregnancy, those whose mothers had migraine without a history of triptan use, and a population comparison group. We also examined longitudinal changes associated with time-varying triptan exposure amongst migraineurs only. Examining longitudinal changes revealed additional differences in exposure groups that were not apparent when children were examined only at 36 months. While externalizing behavior remained elevated from 18 to 36 months, we observed sharply different development in emotionality and activity for prenatally exposed children relative to all comparison groups. Timing of exposure was not as specific as we observed in the first dissertation aim: rather, exposure during either first or second/third trimesters was associated with differences in change from 18 to 36 months, although with wide confidence intervals that included 1.

V.2. Clinical implications

The findings from this dissertation have several implications that could affect providers' clinical management of women who suffer from migraine headache during pregnancy. Previous research focused on pregnancy and delivery outcomes has found an increased risk of spontaneous abortion associated with triptan use during pregnancy,[14] as well as inconsistent associations with preterm birth, pre-eclampsia, and atonic uterus.[12,37] Our work suggests that risks associated with prenatal triptan exposure extend into childhood, and should be considered carefully when recommending treatment options to pregnant women suffering from migraine. These risks should be considered in the context of our, and others', findings that migraine itself carries additional risks.

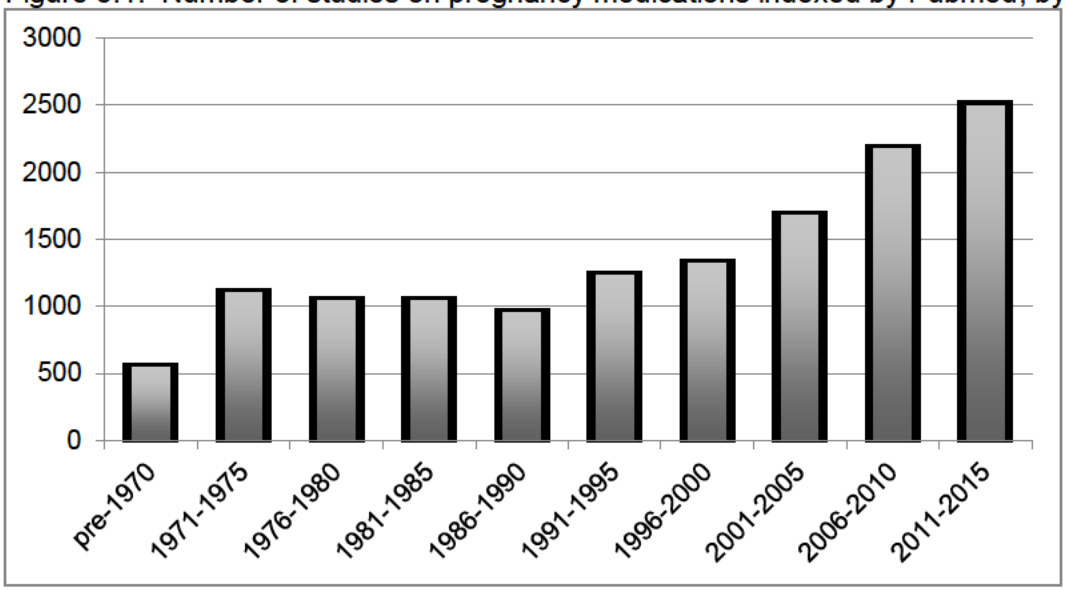
While studies have shown that children with emotional and behavioral problems in early childhood often go on to have academic, social, and psychiatric problems in adolescence,[29,51,99] evidence suggests that early intervention can be successful at ameliorating these risks.[100,101] Understanding that prenatal triptan exposure is a risk factor for emotional and behavioral problems should help to identify children who could benefit from these early interventions.

V.3. Research implications

Awareness of increased medication use during pregnancy has led to increasing attention being paid to the safety of medication use during pregnancy, and the number of studies on this topic has increased sharply in the past decade

(Figure 5.1.). This dissertation has identified several key methodologic areas that may inform future research efforts.

Figure 5.1. Number of studies on pregnancy medications indexed by Pubmed, by year



First, consideration of the role of the underlying condition for which the medication was prescribed is vital to placing risks of medication exposure in context. Construction of appropriate comparison groups is an important first step. A recent meta-analysis of triptan safety in pregnancy noted that several studies could not be included, or that analysis could not be conducted, due to the lack of a migraine-only comparison group.[14] At a minimum, future studies of triptan safety must include comparison groups in which women had migraine headache but did not use triptans. Further, when possible, future studies should include information on migraine severity and type, as these factors may contribute to use of triptan during pregnancy as well as to risk of outcomes in children.

Second, we found that women who used triptans during pregnancy also reported the use of many other medications, including several medication classes that have previously been linked to neurodevelopmental problems in exposed children.[30,31,42–44] Similarly, appropriate modeling of medication use, particularly for medications that are used episodically as triptans are, is essential to obtaining unbiased effect estimates for the risk of medication exposure on pregnancy, delivery, and childhood outcomes. This is especially important when the medication of interest is used in conjunction with other medications, or co-occurs with other potentially harmful exposures.

V.4. Limitations and strengths

Several important limitations indicate that our results should be interpreted with some caution. Selection bias, in the form of high attrition at the 18 and 36-month post-partum follow-up assessment, can result in unpredictable bias of effect estimates, depending on the reasons for attrition. We used inverse probability of censoring weights to adjust our effect estimates for measured predictors of attrition, but residual bias due to unmeasured predictors of attrition is still possible. Relatedly, we used causal inference methods, including marginal structural models and propensity score methods, which make a strong assumption of no unmeasured confounding, which was violated in our study. In addition, while we applied multiple analytic approaches and sensitivity analyses to indirectly control the effects of confounding by migraine severity, and concluded that confounding by migraine severity would have to be unrealistically

strong in order to fully explain our observed effect estimates, we ultimately cannot rule out confounding by indication as an explanation for our results. Finally, despite an initial large sample size, the rarity of triptan exposure in this study meant that we had insufficient power to examine specific triptans, and so analyzed all triptan together as a class. Given differences in formulations, receptor affinity, and pharmacokinetic properties of various triptan medications,[102] it is possible that individual triptans have differences in safety profiles during pregnancy, which we could not examine in this study.

Despite these limitations, this dissertation has several notable strengths that make it a valuable contribution to the literature on the safety of triptan medication exposure during pregnancy. The studies were conducted within the Norwegian Mother and Child Cohort Study (MoBa), a large, prospective birth cohort that includes more than 100,000 mother-child dyads followed from their first ultrasound visit and into childhood.[47] MoBa includes detailed information on medication use during pregnancy, for both prescription and over-the-counter medications. In addition, we used sensitive, psychometrically validated instruments as outcome measures that capture multiple dimensions of child neurodevelopment, including behavior, temperament, psychomotor development, and communication skills. These outcome measures are an improvement over relying on diagnostic codes in the medical record, as the instruments capture neurodevelopmental problems that may not yet rise to the level of a diagnosis, particularly in very young children. Finally, we applied several advanced analytic

techniques, including marginal structural models and propensity matching and calibration, which allowed us to obtain less-biased effect estimates than we would have observed using traditional methods. The findings of this dissertation should be interpreted with these strengths and limitations in mind.

V.5. Final Conclusions

Taken together, the findings from this dissertation suggest that prenatal triptan exposure is associated with consistently elevated externalizing-type behaviors and symptoms, and that these risks are most pronounced for first trimester exposure. While we cannot rule out confounding by indication as an explanation for these findings, our analysis suggests that the effects of migraine severity would have to be extremely strong to fully explain our findings. In light of these results, and also considering previous research,[14] we recommend that triptans be used during pregnancy only if other analgesics do not provide adequate pain relief, and the effects of migraine (nausea, anorexia) are themselves resulting in fetal harm. Future studies should include measures of migraine severity throughout pregnancy, in order to better discern the role of confounding by indication.

REFERENCES

1. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am. J. Obstet. Gynecol.* 2011;205(1):51.e1-8. doi:10.1016/j.ajog.2011.02.029.

2. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. *Am. J. Obstet. Gynecol.* 2004;191(2):398-407. doi:10.1016/j.ajog.2004.04.025.

3. Olesen C, Sørensen HT, de Jong-van den Berg L, Olsen J, Steffensen FH. Prescribing during pregnancy and lactation with reference to the Swedish classification system. A population-based study among Danish women. The Euromap Group. *Acta Obstet. Gynecol. Scand.* 1999;78(2):686-692.

4. Finer LB, Zolna MR. Unintended pregnancy in the United States: Incidence and disparities, 2006. *Contraception* 2011;84(5):478-485. doi:10.1016/j.contraception.2011.07.013.

5. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68(5):343-9. doi:10.1212/01.wnl.0000252808.97649.21.

6. MacGregor EA. Headache in pregnancy. *Neurol. Cinics* 2012;30(3):835-66. doi:10.1016/j.ncl.2012.04.001.

7. Menon R, Bushnell CD. Headache and pregnancy. *Neurologist* 2008;14(2):108-19. doi:10.1097/NRL.0b013e3181663555.

8. Aegidius K, Zwart J-A, Hagen K, Stovner L. The effect of pregnancy and parity on headache prevalence: the Head-HUNT study. *Headache* 2009;49(6):851-9. doi:10.1111/j.1526-4610.2009.01438.x.

9. Chu MK, Buse DC, Bigal ME, Serrano D, Lipton RB. Factors Associated With Triptan Use in Episodic Migraine: Results From the American Migraine Prevalence and Prevention Study. *Headache J. Head Face Pain* 2012;52(2):213-223. doi:10.1111/j.1526-4610.2011.02032.x.

10. Bérard A, Kori S. Dihydroergotamine (DHE) use during gestation and the risk of adverse pregnancy outcomes. *Headache* 2012;52(June 2011):1085-1093. doi:10.1111/j.1526-4610.2012.02172.x.

11. Nezvalová-Henriksen K, Spigset O, Nordeng H. Triptan safety during pregnancy: A Norwegian population registry study. *Eur. J. Epidemiol.* 2013;28:759-769. doi:10.1007/s10654-013-9831-x.

12. Källén B, Nilsson E, Olausson PO. Delivery Outcome after Maternal Use of Drugs for Migraine. *Drug Saf.* 2011;34(8):691-703.

13. Olesen C, Steffensen FH, Sørensen HT, Nielsen GL, Olsen J. Pregnancy outcome following prescription for sumatriptan. *Headache* 2000;40:20-24. doi:10.1046/j.1526-4610.2000.00003.x.

14. Marchenko A, Etwel F, Olutunfese O, Nickel C, Koren G, Nulman I. Pregnancy Outcome Following Prenatal Exposure to Triptan Medications: A Meta-Analysis. *Headache J. Head Face Pain* 2015:n/a-n/a. doi:10.1111/head.12500.

15. Amundsen S, Nordeng H, Nezvalova-Henriksen K, Stovner L, Spigset O. Pharmacological treatment of migraine during pregnancy and breastfeeding - current evidence and practical recommendations. *Nat. Rev. Neurol.*

16. Ferrari M, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22:633-658.

17. Oberlander TF, Gingrich JA, Ansorge MS. Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. *Clin. Pharmacol. Ther.* 2009;86(6):672-7. doi:10.1038/clpt.2009.201.

18. Bonnin A, Levitt P. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. *Neuroscience* 2011;197:1-7. doi:10.1016/j.neuroscience.2011.10.005.

19. Bonnin A, Torii M, Wang L, Rakic P, Levitt P. Serotonin modulates the response of embryonic thalamocortical axons to netrin-1. *Nat. Neurosci.* 2007;10(5):588-597. doi:10.1038/nn1896.

20. Bonnin A, Levitt P. Placental Source for 5-HT that Tunes Fetal Brain Development. *Neuropsychopharmacology* 2012;37(1):299-300. doi:10.1038/npp.2011.194.

21. Clerkin SM, Schulz KP, Berwid OG, et al. Thalamo-cortical activation and connectivity during response preparation in adults with persistent and

remitted ADHD. *Am. J. Psychiatry* 2013;170(September):1011-1019. doi:10.1176/appi.ajp.2013.12070880.

22. Morgan VA, Croft ML, Valuri GM, et al. Intellectual disability and other neuropsychiatric outcomes in high-risk children of mothers with schizophrenia, bipolar disorder and unipolar major depression. *Br. J. Psychiatry* 2012;200(4):282-9. doi:10.1192/bjp.bp.111.093070.

23. McManus BM, Poehlmann J. Parent-child interaction, maternal depressive symptoms and preterm infant cognitive function. *Infant Behav. Dev.* 2013;35(3):489-498. doi:10.1016/j.infbeh.2012.04.005.Parent-child.

24. Newacheck PW, Kim SE. A national profile of health care utilization and expenditures for children with special health care needs. *Arch. Pediatr. Adolesc. Med.* 2005;159(1):10-7. doi:10.1001/archpedi.159.1.10.

25. Sices L, Harman JS, Kelleher KJ. Health-care use and expenditures for children in special education with special health-care needs: is dual classification a marker for high use? *Public Health Rep.* 2007;122(4):531-40.

26. Bosco JLF, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J. Clin. Epidemiol.* 2010;63(1):64-74. doi:10.1016/j.jclinepi.2009.03.001.

27. Gasparini CF, Sutherland HG, Griffiths LR. Studies on the pathophysiology and genetic basis of migraine. *Curr. Genomics* 2013;14(5):300-15. doi:10.2174/13892029113149990007.

28. Ligthart L, Nyholt DR, Penninx BWJH, Boomsma DI. The shared genetics of migraine and anxious depression. *Headache* 2010;50:1549-1560. doi:10.1111/j.1526-4610.2010.01705.x.

29. Beyer T, Postert C, Müller JM, Furniss T. Prognosis and continuity of child mental health problems from preschool to primary school: results of a four-year longitudinal study. *Child Psychiatry Hum. Dev.* 2012;43:533-43. doi:10.1007/s10578-012-0282-5.

30. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment : a sibling-controlled cohort study. *Int. J. Epidemiol.* 2013;42:1702-13. doi:10.1093/ije/dyt183.

31. Liew Z, Ritz B, Rebordosa C, Lee P-C, Olsen J. Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders. *JAMA Pediatr.* 2014;168(4):313-320. doi:10.1001/jamapediatrics.2013.4914.

32. Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics* 2010;125(3):e600-8. doi:10.1542/peds.2008-3655.

33. Oberlander TF, Reebye P, Misri S, Papsdorf M, Kim J, Grunau RE. Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. *Arch. Pediatr. Adolesc. Med.* 2007;161(1):22-9. doi:10.1001/archpedi.161.1.22.

34. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. *Eur. J. Neurol. Off. J. Eur. Fed. Neurol. Soc.* 2009;16(9):968-81. doi:10.1111/j.1468-1331.2009.02748.x.

35. Shuhaiber S, Pastuszak A, Schick B, et al. Brief Communications Pregnancy outcome following first trimester exposure to sumatriptan. *Neurology* 1998;5:581-583.

36. O'Quinn S, Ephross SA, Williams V, Davis RL, Gutterman DL, Fox AW. Pregnancy and perinatal outcomes in migraineurs using sumatriptan: a prospective study. *Arch. Gynecol. Obstet.* 1999;263(1-2):7-12.

37. Nezvalová-Henriksen K, Spigset O, Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. *Headache* 2010;50(4):563-75. doi:10.1111/j.1526-4610.2010.01619.x.

38. Petty CR, Rosenbaum JF, Hirshfeld-Becker DR, et al. The Child Behavior Checklist broad-band scales predict subsequent psychopathology: a five-year follow-up. *J. Anxiety Disord.* 2008;22(3):532-539.

39. Mathyssek CM, Olino TM, Verhulst FC, van Oort FV A. Childhood internalizing and externalizing problems predict the onset of clinical panic attacks over adolescence: the TRAILS study. *PLoS One* 2012;7(12):e51564. doi:10.1371/journal.pone.0051564.

40. Evans EW, Lorber KC. Use of 5-HT1 agonists in pregnancy. *Ann. Pharmacother.* 2008;42(4):543-9. doi:10.1345/aph.1K176.

41. Tfelt-Hansen PC. Does sumatriptan cross the blood-brain barrier in animals and man? *J. Headache Pain* 2010;11(1):5-12. doi:10.1007/s10194-009-0170-y.

42. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *Br. Med. J.* 2013;346:f2059-f2059. doi:10.1136/bmj.f2059.

43. Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch. Gen. Psychiatry* 2011;68(11):1104-12. doi:10.1001/archgenpsychiatry.2011.73.

44. Figueroa R. Use of antidepressants during pregnancy and risk of attention-deficit/hyperactivity disorder in the offspring. *J. Dev. Behav. Pediatr.* 2010;31(8):641-648. doi:10.1097/DBP.0b013e3181e5ac93.

45. Clements CC, Castro VM, Blumenthal SR, et al. Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Mol. Psychiatry* 2014;(April):1-8. doi:10.1038/mp.2014.90.

46. Stoltenberg C, Schjølberg S, Bresnahan M, et al. The Autism Birth Cohort (ABC): a paradigm for gene-environment-timing research. *Mol. Psychiatry* 2010;15(7):676-680. doi:10.1038/mp.2009.143.THE.

47. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int. J. Epidemiol.* 2006;35(5):1146-50. doi:10.1093/ije/dyl170.

48. Classifications: The anatomical-therapeutic chemical classification system with defined daily doses (ATC/DDD). *World Heal. Organ.* 2012. Available at: www.who.int/classifications/atcddd/en.

49. Newport DJ, Brennan PA, Green P, et al. Maternal depression and medication exposure during pregnancy: comparison of maternal retrospective recall to prospective documentation. *Br. J. Obstet. Gynaecol.* 2008;115(6):681-8. doi:10.1111/j.1471-0528.2008.01701.x.

50. Van Gelder MMHJ, van Rooij IALM, de Walle HEK, Roeleveld N, Bakker MK. Maternal Recall of Prescription Medication Use During Pregnancy Using a Paper-Based Questionnaire. *Drug Saf.* 2013;36:43-54. doi:10.1007/s40264-012-0004-8.

51. Pihlakoski L, Sourander A, Aromaa M, Rautava P, Helenius H, Sillanpää M. The continuity of psychopathology from early childhood to preadolescence: a prospective cohort study of 3-12-year-old children. *Eur. Child Adolesc. Psychiatry* 2006;15(7):409-17. doi:10.1007/s00787-006-0548-1.

52. Nøvik TS. Validity of the Child Behaviour Checklist in a Norwegian sample. *Eur. Child Adolesc. Psychiatry* 1999;8(4):247-54.

53. Fink P, Ørnbøl E, Hansen MS, Søndergaard L, De Jonge P. Detecting mental disorders in general hospitals by the SCL-8 scale. *J. Psychosom. Res.* 2004;56(3):371-375. doi:10.1016/S0022-3999(03)00071-0.

54. Marino E, Fanny B, Lorenzi C, et al. Genetic bases of comorbidity between mood disorders and migraine: possible role of serotonin transporter gene. *Neurol. Sci.* 2010;31(3):387-91. doi:10.1007/s10072-009-0183-y.

55. Carlo W. Prematurity and intrauterine growth restriction. In: Kleigman R, Behrman R, Jenson H, Stanton B, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadephia, PA: Elsevier; 2011.

56. Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. Springer; 2009.

57. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache* 2013;53(3):427-36. doi:10.1111/head.12074.

58. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am. J. Epidemiol.* 2004;159(7):702-706. doi:10.1093/aje/kwh090.

59. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000;11(5):561-70.

60. Robins JM, Hernan M, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-560.

61. Bodnar LM, Sunder KR, Wisner KL. Treatment with selective serotonin reuptake inhibitors during pregnancy: deceleration of weight gain because of depression or drug? *Am. J. Psychiatry* 2006;163(6):986-991. doi:10.1176/appi.ajp.163.6.986.

62. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am. J. Epidemiol.* 2008;168(6):656-64. doi:10.1093/aje/kwn164.

63. Valeri L, Vanderweele TJ. Mediation Analysis Allowing for Exposure-Mediator Interactions and Causal Interpretation: Theoretical Assumptions and Implementation With SAS and SPSS Macros. *Psychol. Methods* 2013;18(2):137-150. doi:10.1037/a0031034.

64. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatr.* 2005;94(1):2-15.

65. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *J. Am. Acad. Child Adolesc. Psychiatry* 2014;53(1):34-46.e2. doi:10.1016/j.jaac.2013.09.001.

66. Lavigne J V, Arend R, Rosenbaum D, Binns HJ, Christoffel KK, Gibbons RD. Psychiatric disorders with onset in the preschool years: I. Stability of diagnoses. *J. Am. Acad. Child Adolesc. Psychiatry* 1998;37(12):1246-54. doi:10.1097/00004583-199812000-00007.

67. Cox HC, Lea RA, Bellis C, et al. Heritability and genome-wide linkage analysis of migraine in the genetic isolate of Norfolk Island. *Gene* 2012;494(1):119-23. doi:10.1016/j.gene.2011.11.056.

68. Arruda MA, Bigal ME. Migraine and behavior in children: influence of maternal headache frequency. *J. Headache Pain* 2012;13(5):395-400. doi:10.1007/s10194-012-0441-x.

69. Stam AH, de Vries B, Janssens A CJW, et al. Shared genetic factors in migraine and depression: evidence from a genetic isolate. *Neurology* 2010;74(4):288-94. doi:10.1212/WNL.0b013e3181cbcd19.

70. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr. Perinat. Epidemiol.* 2009;23(6):597-608. doi:10.1111/j.1365-3016.2009.01062.x.

71. Salvadori F, Gelmi V, Muratori F. Present and previous psychopathology of juvenile onset migraine: a pilot investigation by Child Behavior Checklist. *J. Headache Pain* 2007;8(1):35-42. doi:10.1007/s10194-007-0334-y.

72. Ystrom E, Vollrath ME, Nordeng H. Effects of personality on use of medications, alcohol, and cigarettes during pregnancy. *Eur. J. Clin. Pharmacol.* 2012;68(5):845-51. doi:10.1007/s00228-011-1197-y.

73. Jang K, Livesley W, Vernon P. Heritability of the big five personality dimensions and their facets: a twin study. *J. Pers.* 1996;64(3):577-91.

74. Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior and personality: Modeling the externalizing spectrum. *J. Abnorm. Psychol.* 2002;111(3):411-424.

75. Moffitt TE. Genetic and environmental influences on antisocial behaviors: evidence from behavioral-genetic research. *Adv. Genet.* 2005;55(05):41-104. doi:10.1016/S0065-2660(05)55003-X.

76. Duong S, Nordeng H, Einarson A. Motherisk Update Safety of triptans for migraine headaches during pregnancy and breastfeeding. *Can. Fam. Physician* 2010;56:537-539.

77. Wood ME, Lapane K, Frazier JA, Ystrom E, Mick E, Nordeng H. Prenatal triptan exposure increases externalizing behaviors at three years: results from the Norwegian Mother and Child Cohort Study. *Manuscr. under Rev.*

78. Magnus P. The Norwegian Mother and Child Cohort Study (MoBa) – new research possibilities. *Nor. Epidemiol.* 2007;17(2):107-110.

79. Klein DN, Kotov R, Bufferd SJ. Personality and depression: explanatory models and review of the evidence. *Annu. Rev. Clin. Psychol.* 2011;7:269-295. doi:10.1146/annurev-clinpsy-032210-104540.

80. Althoff RR, Rettew DC, Faraone S V, Boomsma DI, Hudziak JJ. Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biol Psychiatry* 2006;60(9):903-911. doi:S0006-3223(06)00300-3 [pii] 10.1016/j.biopsych.2006.02.025.

81. Mathiesen KS, Tambs K. The EAS Temperament Questionnaire--factor structure, age trends, reliability, and stability in a Norwegian sample. *J. Child Psychol. Psychiatry* 1999;40:431-439.

82. Halbwachs M, Muller J-B, Tich SN, et al. Predictive Value of the Parent-Completed ASQ for School Difficulties in Preterm-Born Children < 35 Weeks' GA at Five Years of Age. *Neonatology* 2014;106:311-316. doi:10.1159/000363216.

83. Grissmer D, Grimm KJ, Aiyer SM, Murrah WM, Steele JS. Fine motor skills and early comprehension of the world: two new school readiness indicators. *Dev. Psychol.* 2010;46(5):1008-1017. doi:10.1037/a0020104.

84. Richter J, Janson H. A validation study of the Norwegian version of the Ages and Stages Questionnaires. *Acta Paediatr.* 2007;96(5):748-52. doi:10.1111/j.1651-2227.2007.00246.x.

85. Amundsen S, Skretteberg AM, Gudmestad T, Buckley Poole AC, Nordeng H. Patients with migraine in pregnancy: pharmacological treatment, perceived disease control and information needs. *under Rev.*

86. Hasnaoui A El, Vray M, Richard A, Nachit-Ouinekh F, Boureau F, Group M. Assessing the Severity of Migraine: Development of the MIGSEV Scale. *Headache J. Head Face Pain* 2003;43:628-635.

87. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol. Health* 1999;14(1):1-24. doi:10.1080/08870449908407311.

88. Jónsdóttir H, Friis S, Horne R, Pettersen KI, Reikvam Å, Andreassen O a. Beliefs about medications: Measurement and relationship to adherence in patients with severe mental disorders. *Acta Psychiatr. Scand.* 2009;119(4):78-84. doi:10.1111/j.1600-0447.2008.01279.x.

89. Stürmer T, Schneeweiss S, Avorn J, Glynn RJ. Adjusting effect estimates for unmeasured confounding with validation data using propensity score calibration. *Am. J. Epidemiol.* 2005;162(3):279-89. doi:10.1093/aje/kwi192.

90. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia* 2009;29(3):286-92. doi:10.1111/j.1468-2982.2008.01704.x.

91. Marozio L, Facchinetti F, Allais G, et al. Headache and adverse pregnancy outcomes: a prospective study. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 2012;161(2):140-3. doi:10.1016/j.ejogrb.2011.12.030.

92. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. *Dev. Neurosci.* 2009;31(4):285-92. doi:10.1159/000216539.

93. Lunt M, Glynn RJ, Rothman KJ, Avorn J, Stürmer T. Propensity score calibration in the absence of surrogacy. *Am. J. Epidemiol.* 2012;175(12):1294-302. doi:10.1093/aje/kwr463.

94. Stürmer T, Schneeweiss S, Rothman KJ, Avorn J, Glynn RJ. Performance of propensity score calibration- a simulation study. *Am. J. Epidemiol.* 2007;165(10):1110-1118.

95. Wood ME, Nordeng H, Frazier JA, Lapane K. Prenatal triptan exposure and early childhood neurodevelopmental outcomes: an application of propensity score calibration to adjust for unmeasured confounding by migraine severity. *Manuscr. Prep.*

96. Aubé M. Migraine in pregnancy. *Neurology* 1999;53(4 Suppl 1):S26-8.

97. Robins JM. Association, causation, and marginal structural models. *Synthese* 1999;121:151-179.

98. Sourander A, Helstelä L, Helenius H. Parent-adolescent agreement on emotional and behavioral problems. *Soc. Psychiatry Psychiatr. Epidemiol.* 1999;34:657-663. doi:10.1007/s001270050189.

99. Holtmann M, Buchmann AF, Esser G, Schmidt MH, Banaschewski T, Laucht M. The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. *J. Child Psychol. Psychiatry.* 2011;52(2):139-147. doi:10.1111/j.1469-7610.2010.02309.x.

100. Feinfield KA, Baker BL. Empirical support for a treatment program for families of young children with externalizing problems. *J. Clin. Child Adolesc. Psychol.* 2004;33(1):182-95. doi:10.1207/S15374424JCCP3301_17.

101. Bagner DM, Sheinkopf SJ, Vohr BR, Lester BM. Parenting intervention for externalizing behavior problems in children born premature: An intial examination. *J. Dev. Behav. Pediatr.* 2010;31(3):209-216. doi:10.1097/DBP.0b013e3181d5a294.Parenting.

102. Jhee SS, Shiovitz T, Crawford a W, Cutler NR. Pharmacokinetics and pharmacodynamics of the triptan antimigraine agents: a comparative

review. *Clin. Pharmacokinet.* 2001;40(3):189-205. doi:10.2165/00003088-200140030-00004.

103. Pedersen LH, Henriksen TB, Bech BH, Licht RW, Kjaer D, Olsen J. Prenatal antidepressant exposure and behavioral problems in early childhood--a cohort study. *Acta Psychiatr. Scand.* 2013;127(2):126-35. doi:10.1111/acps.12032.