Johanne Naper Trønnes

Medication safety in pregnancy

With focus on analgesics and neurodevelopmental outcomes in children

Thesis submitted for the degree of Philosophiae Doctor

Department of Pharmacy
Faculty of Mathematics and Natural Sciences

PharmacoEpidemiology and Drug Safety Research Group
PharmaTox Strategic Research Initiative

UNIVERSITY OF OSLO

2022

Series of dissertations submitted to the
Faculty of Mathematics and Natural Sciences, University of Oslo
No. 2525

ISSN 1501-7710

Cover: Hanne Baadsgaard Utigard.
Print production: Graphics Center, University of Oslo.

Preface

This thesis is submitted in partial fulfillment of the requirements for the degree of *Philosophiae Doctor* at the University of Oslo. The research presented here has been conducted under the supervision of Professor Hedvig Nordeng and Dr. Angela Lupattelli.

The thesis is a collection of four papers, presented in chronological order of writing. The central theme is medication safety in pregnancy – with focus on analgesics and neurodevelopmental outcomes in children. All papers represent joint work with the supervisors and other collaborators. The thesis synopsis consists of an introductory chapter that provides background information and motivation for the research. This is followed by the thesis aims, materials and methods, main findings, discussion, conclusions, and perspectives. Copies of the papers are included in this thesis.

Acknowledgements

I want to thank all those women who participated in the Multinational Medication Use in Pregnancy Study and in the Norwegian Mother, Father, and Child Cohort Study. Without them, it would not have been possible to carry out the studies for this thesis.

I would like to express my gratitude to my supervisors Professor Hedvig Nordeng and Dr. Angela Lupattelli for introducing me to the field of perinatal pharmacoepidemiology. Thank you both for entrusting me with such an interesting research project, for your expertise and encouragement. Hedvig, thank you for sharing your passion for this research field. Angela, your day-to-day help and support has been invaluable to me during these research years.

Thanks to all my co-authors for great collaborations. Thanks to Dr. Mollie Wood for our conversations about propensity scores and bias. Thanks to Professor Eivind Ystrøm for introducing me to psychometric scales. Thanks to Dr. Marte Handal and Dr. Svetlana Skurtveit for fruitful discussions and scientific advice.

I owe gratitude to the European Research Council (ERC) for funding the PhD research project. I also acknowledge The PharmaTox Strategic Research Initiative, the Norwegian Pharmaceutical Association (NFS), the Norwegian PhD School of Pharmacy (NFIF), and the National research school in population based

epidemiology (EPINOR) for financial support. This enabled me to attend relevant courses and conferences, and for that, I am grateful.

I would also like to thank all the members of the PharmaSafe Research Group for an enjoyable working environment. Thanks to those of you who proof-read my thesis. Thanks to Bich and Gerd-Marie, we started this journey together and I am very grateful for sharing it with both of you. Thank you for all the nice conversations and laughs we had in the office together. A special thanks to Gerd-Marie, for your encouragement during the write-up of our theses. I would also like to thank Sarah, for always having the time to talk and for your advice.

Finally, I would like to thank my family and friends for their support throughout this PhD period. It has been quite a journey and I have grown and learned so much. A special thanks to Kim, you are my best friend and partner. I could not have done this without your love and endless support. Thanks to my two beautiful children, Jacob and Niklas, you mean the world to me.

Johanne Naper Trønnes

Oslo, March 2022

Table of Contents

Abstract

Background: The majority of women report medication use during pregnancy and analgesics rank amongst the most frequently used (50-70% of pregnancies). We need to generate knowledge that can fill the knowledge gaps about medication safety in pregnancy, to ensure safe use of medications. Studies investigating the association between prenatal exposure to analgesics and neurodevelopmental outcomes in children are either lacking or inconclusive. Given the widespread use of analgesics, a potential adverse effect on child neurodevelopment would have huge implications for public health.

Aim: The overall aim of this thesis was two-fold. First, to explore the safety profile of medication used during pregnancy. Second, to extend our understanding of the safety of prenatal exposure to two commonly used analgesics (paracetamol and opioids), on offspring neurodevelopment. The specific aims were to 1) explore the safety profile of medication used during pregnancy and to identify factors associated with the use of potentially risky medication (paper I), 2) explore the association between prenatal exposure to paracetamol and communication skills, behavior and temperament in preschool-aged children (paper II), 3) examine the association between prenatal exposure to opioid analgesics and attention-deficit/hyperactivity disorder (ADHD) in children (paper III), and 4) investigate the association between prenatal exposure to opioid analgesics and scholastic skills in fifth grade (paper IV).

Methods: Aim I was addressed by using data from the Multinational Medication Use in Pregnancy Study, including pregnant women and women who had given birth in the previous year from 15 European countries. Multiple risk classification systems were used to evaluate medication safety. To address aims II-IV, data from the Norwegian Mother, Father, and Child Cohort study (MoBa), which includes data on self-reported medication use, was linked to the Medical Birth Registry of Norway (MBRN). Data on ADHD diagnosis and prescription ADHD medications were obtained from the Norwegian Patient Register and the Norwegian Prescription Database, respectively and linked to the two previously mentioned datasets to address aim III. For aim IV, data on national school test results (provided by Statistics Norway) were linked to MoBa and MBRN. Propensity score based methods with weighting were used to control confounding in papers II-IV. Multiple imputation was used to handle missing data in papers III and IV.

Results: Based on a study population of 6657 participants, paper I showed that the majority of women (69%) used medications classified as safe to use during pregnancy, and 28% used medication classified as potentially risky. We observed

geographical differences with respect to the use of medications in different risk groups. Both medical and sociodemographic factors were associated with the use of potentially risky medications. Having a chronic disorder was the factor strongest associated with the use of potentially risky medications. One out of five medications used could not be assigned any risk category in pregnancy.

Paper II included 32 934 mother-child pairs. Timing of exposure to paracetamol, as well as short-term exposure during pregnancy, was not associated with an increased risk of communication, behavior or temperamental problems in preschool-aged children. Prenatal exposure to paracetamol in multiple trimesters was associated with lower scores on shyness (two trimesters, β: −0.62, 95% CI: −1.05, −0.19) and increased internalizing (three trimesters, relative risk (RR): 1.36, 95% CI: 1.02, 1.80) and externalizing behavior (three trimesters, RR: 1.22, 95% CI: 0.93, 1.60) in pre-school aged children, compared to children with no exposure.

Paper III was based on two study populations, which consisted of data on ADHD diagnosis (73 480 mother-child pairs) and ADHD symptoms at child age 5 years (31 270 mother-child pairs). Approximately 2.1% of women were exposed to an opioid analgesic anytime during pregnancy. We did not identify any association between timing of prenatal exposure to opioid analgesics and ADHD diagnosis or symptoms. Prenatal exposure for 5 or more weeks was associated with an increased risk of ADHD diagnosis (Hazard Ratio (HR): 1.60, 95% CI: 1.04, 2.47) compared with exposure for 4 weeks or less. There was no such association for the risk of ADHD symptoms.

Among the 64 256 children included in paper IV, we found that children exposed to opioid analgesics in the first trimester and those exposed for longer duration scored lower than children of mothers with only pre-pregnancy exposure on tests in literacy and numeracy (β: −0.14, 95% CI: −0.25, −0.04 and β: −0.19, 95% CI: −0.34, −0.05). The clinical meaning of these differences is uncertain.

Conclusions: Overall, findings from this thesis were reassuring. The majority of women used medication classified as safe to use during pregnancy. We did not find evidence of associations between timing or short–term use of paracetamol and adverse neurodevelopmental problems in preschool-aged children. Prenatal exposure to opioid analgesics did not seem to increase the risk of ADHD, or substantially negatively affect scholastic performance in fifth grade, although a possible duration effect for ADHD cannot be ruled out. Adequate pain management in pregnancy should be discussed on an individual patient level, bearing in mind the benefits and risks of different analgesic therapies.

List of Papers

Paper I

Trønnes, J.N., Lupattelli, A. and Nordeng, H. "Safety profile of medication used during pregnancy: Results of a multinational European study". In: *Pharmacoepidemiol Drug Saf* vol. 26, no. 7 (2017), pp. 802-811.

Paper II

Trønnes. J.N., Wood, M., Lupattelli, A., Ystrom, E. and Nordeng, H. "Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 247-256.

Paper III

Trønnes, J.N., Lupattelli, A., Handal, M., Skurtveit, S., Ystrom, E. and Nordeng, H. "Association of timing and duration of prenatal analgesic opioid exposure with attention-deficit/hyperactivity disorder in children". In: *JAMA Netw Open* vol 4. no. 9 (2021), pp. e2124324.

Paper IV

Trønnes, J.N., Lupattelli, A., Ystrom, E. and Nordeng, H. "Prenatal exposure to opioid analgesics and scholastic skills in fifth grade – a follow up study in the Norwegian Mother, Father, and Child Cohort". *Submitted for publication.*

List of Figures

List of Tables

Abbreviations

ACRONYMS

ADHD	Attention-Deficit/Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CI	Confidence Interval
CPRS-R (S)	Conners' Parent Rating Scale-Revised, Short Form
DAGs	Directed Acyclic Graphs
FDA	Food and Drug Administration
GW	Gestational Week
HR	Hazard Ratio
ICD	International Classification of Diseases
IPTW	Inverse Probability of Treatment Weight
MME	Morphine Milligram Equivalent
OR	Odds Ratio
OTC	Over The Counter
PS	Propensity Score
RCT	Randomized Controlled Trial
RR	Relative Risk
SCL-5	The Hopkins Symptoms Checklist (5 items)
SMR	Standardized Mortality/Morbidity Ratio weights
SD	Standard Deviation

DATA SOURCES

MBRN	Medical Birth Registry of Norway
MoBa	Norwegian Mother, Father, and Child Cohort
NorPD	Norwegian Prescription Database
NPR	Norwegian Patient Register
SSB	Statistics Norway

1 Introduction

Today, the majority of women use medications during pregnancy, and analgesics rank amongst the most frequently used [1-3]. To ensure safe use of medications among pregnant women, we need to generate sound knowledge about their safety. Knowledge about the impact of analgesic use in pregnancy on maternal-child health is fundamental to making informed and evidence based decisions when treating women with pain during pregnancy.

Risk classification systems, e.g. the Swedish classification system, place medications in groups according to their safety profile [4]. These classification systems may be used to study medication utilization patterns at an aggregated level and to identify potentially harmful practices [4, 5]. Medication utilization patterns may change over time, and such use needs to be continuously monitored [2]. However, medication utilization studies use different methods to assess medication exposure, different safety classification systems, and assess different types of medications, making comparison across studies and countries difficult [2]. Multinational studies could overcome some of the mentioned challenges.

Due to exclusion of pregnant women from pre-clinical trials, information about medication safety in pregnancy is often inadequate [6]. Studies of medication safety in pregnancy rely on observational data and have until recently focused on immediate birth outcomes [6]. The reproductive safety of a medication cannot be assured without considering long-term effects on the child. It is mainly within the last decade that neurodevelopmental outcomes in offspring have gained awareness [7]. Given the widespread use of analgesics (between 50 to 70% of pregnancies [3, 8]), any potential adverse effect on child neurodevelopment would have huge implications for public health. Studies investigating the association between prenatal exposure to analgesics and neurodevelopmental outcomes in children is either lacking or inconclusive.

This thesis focuses on understanding the safety profile of medication used during pregnancy using multiple risk classification systems, and to further determine the reproductive safety of analgesics on neurodevelopmental outcomes in the offspring. The next section will introduce how medication safety in pregnancy became a public health concern.

1.1 Historical perspectives

Until the middle of the 20th century there was a general belief among medical professionals that the placenta acted as an impermeable barrier to harmful substances and that the fetus was protected in the womb [9]. This belief was challenged by the "thalidomide-disaster" in the 1960s [6]. Thalidomide was a hypnotic/sedative medication prescribed to pregnant women in the late 1950s and beginning of the 1960s to manage morning sickness. Thalidomide was described as a medication with no risk for pregnant women [10]. However, in 1961, two independent researchers discovered a link between the use of thalidomide during pregnancy and severe limb malformations and other anomalies in babies [10]. By that time, more than 10 000 infants worldwide were affected [10].

The discovery called attention to medication safety in pregnancy and opened a new research field in prenatal exposure to medications and negative birth outcomes [6]. To date, medication safety in pregnancy research has mainly focused on immediate birth outcomes, such as malformations, preterm birth, and birthweight. However, in the beginning of the 1970s prenatal exposure to medications was also linked to long-term consequences for child health. The first case that demonstrated this involved the medication diethylstilbestrol, which was prescribed to pregnant women for the prevention of spontaneous abortions [11]. Herbst et al. [11] described an association between the use of diethylstilbestrol during pregnancy and increased risk of adenocarcinoma of the vagina in patients aged 15-22 years.

It is mainly within the last decade that long-term effects after prenatal exposure to medications have received increased attention. In particular, valproic acid stands out with accumulating evidence relating to neurobehavioral effects [12, 13]. Because of this, increased research focus has been placed on investigating other medications acting in the central nervous system and their effect on child neurodevelopment [12, 14], e.g. antidepressants, analgesic opioids, and benzodiazepines.

Because of the thalidomide disaster, drug regulations were changed and strengthened the need of post-authorization medication safety surveillance systems and requirements for pre-clinical testing of medications in different animal models [6]. The U.S. Food and Drug Administration (FDA) implemented guidelines that excluded women of childbearing potential and pregnant women from clinical trials in order to avoid potential harm to the fetus [15]. Thus, many medications have been placed on the marked with inadequate or limited safety data available on the use among pregnant women. Of 172 medications approved by the FDA between 2000 and 2010, only four (2%) could be assigned a specific teratogenic risk, and there

was no existing human data to assess the teratogenic risk for 126 (73%) of the approved medications [16].

1.2 Risk assessment

Because pregnant women are routinely excluded from randomized controlled trials (RCT), safety data often rely on animal studies or post-marketing observational studies. Animal data may provide information and signals about potential teratogenic effects, but these results are not always transferable to humans [17]. For instance, while thalidomide was not found to exert teratogenic effects in rats, it did cause malformations in rabbits, highlighting the difference of species-specific mechanisms of teratogenicity [15]. Observational studies provide real-world data, and are playing an increasing role in regulatory decisions [18].

Taking a medication in pregnancy involves weighing the risk versus benefits for both mother and child [19]. There exist a general skepticism towards the use of medications in pregnancy. Many pregnant women avoid taking prescribed medications in fear of harming the unborn child and prefer to cope with the illness rather than taking a medication. However, pharmacological therapy may be needed to ensure maternal-fetal health [20]. Risk assessment is complex [21], partly because there are many medications and a range of potential outcomes to investigate [22].

Different risk classification systems have been established to provide guidance to healthcare professionals when counselling pregnant women about the safety of medications in pregnancy. These systems place medications in groups based on their safety profile [4]. The most well-known classification systems include the Swedish classification system (FASS) [23], the FDA classification system [24], and the Australian classification system [25]. All classification systems use letter categories to assign safety (Table 1.1), and classifications are based on available clinical data [4]. The risk classification systems are of value when describing and monitoring medication utilization patterns during pregnancy at a population level. Although these systems use almost the same letter codes, their contents are different. A recent study by Addis et al. [4] showed that only 26% of medications common to all three systems were placed in the same risk category. In 2015, FDA ruled to change the labelling system and replace the letter-based classification system with more narrative sections that provide explanations based on available information, including information from observational pharmacoepidemiological studies [26].

Furthermore, several initiatives have been established to improve pregnancy-related medication safety information, including pregnancy exposure registries [27] and

specialized Teratology Information Services (TIS) [22, 28]. The latter may provide individual based risk assessment and counseling to pregnant women and to healthcare professionals.

Table 1.1 Description of risk groups by the various pregnancy risk classification systems.

	Safety category	Definition
Swedish	A	Medications taken by a large number of pregnant women with no proven increase in the frequency of malformations or other observed harmful effects on the fetus.
	B1	Limited experience in pregnant women, no increase observed in the frequency of malformations or other observed harmful effects on the fetus. Animal studies reassuring.
	B2	Limited experience in pregnant women, no increase observed in the frequency of malformations or other harmful effects on the fetus. Animal studies inadequate or lacking.
	B3	Limited experience in pregnant women, no increase observed in the frequency of malformations or other harmful effects on the fetus. Animal studies have shown evidence of an increased occurrence of fetal damage.
	C	May cause pharmacological adverse effects on the fetus or neonate.
	D	Suspected or proven to cause malformations or other irreversible damage on the fetus.
Australian	A-D	Categories A – D similar to the Swedish definitions.
	X	High risk of causing permanent damage to the fetus. Contraindicated in pregnancy.
FDA	A	Controlled studies fail to demonstrate a risk to the fetus in the first trimester.
	B	No controlled studies in humans, animal studies indicate no risk. Well-controlled studies in humans show no risk, and animal studies show an adverse effect on the fetus.
	C	No controlled studies in women. Animal studies indicate risk or are lacking.
	D	Existing evidence of fetal risk in humans, benefits may outweigh risks in certain situations.
	X	Risk clearly outweighs any possible benefit. Contraindicated in pregnancy.

FDA, the U.S. Food and Drug Administration. Information obtained from [23, 25, 29].

1.3 Introduction to and prevalence of medication use during pregnancy

Today, women become pregnant at an older age than before [30]. A higher mean age at conception may increase the risk of obstetric and perinatal complications, and the likelihood of having a pre-existing medical condition that demand medical

attention [31]. Furthermore, many physiological changes takes place in the woman's body during pregnancy. Some of the most common pregnancy-related discomforting ailments include nausea and vomiting, headache, heartburn, constipation and pelvic girdle pain [31]. Short- or long-term pharmacotherapy may be needed to ensure maternal-fetal health.

Indeed, medication use is common during pregnancy and has increased during the last decades [2, 32, 33]. Studies based on filled prescriptions in pregnancy indicate prevalence estimates ranging from 60% [33] to 90% [8]. The latter estimate also captured prenatal vitamins and minerals [8]. In a multinational study from 2014, it was estimated that 8 out of 10 women use at least one medication during pregnancy [3]. This information was collected using a web-based questionnaire and included self-reported medication use, either prescribed or over-the-counter (OTC) medication. The most frequently used medication groups included analgesics, antacids, nasal decongestants and systemic antibiotics [3].

Studies have also tried to estimate the prevalence of use of medications with a potential for fetal harm among pregnant women [2]. Prevalence estimates vary between countries. Table 1.2 shows examples of recent studies examining the safety profile of medication used during pregnancy. A recent study by Blotière et al [34], estimated that 2.2% of pregnant women in France were exposed to a potentially harmful medication when the Swedish classification system were used, and most commonly doxycycline, erythromycin, and ondansetron. In the study by Raichand et al. [35], 2.0% of women in Australia were exposed to a medication with potential for fetal harm when the Australian classification system was used, and most commonly doxycycline, paroxetine and valproate.

Overall, studies have consistently reported the use of potentially risky medications during pregnancy. The variation may be attributed to differences in the study methods used to assess medication exposure and to the different classification systems used. This makes comparison of results challenging. Medication utilization patterns may change over time and such use needs to be monitored in order to ensure safe medication use for both mother and child [36]. Furthermore, Thorpe et al. [5] highlighted that the data available for assessing the risk is insufficient for most commonly used medications in pregnancy. In that study, only two out of the 54 medications evaluated had "good to excellent" data available to assess teratogenic risk according to Teratology Information System (TERIS).

Table 1.2 Examples of studies examining the safety profile of medication used during pregnancy.

Author (year)	**Country Study period**	**Design, exposure ascertainment**	**Sample size**	**Risk classification system**	**Main findings** Prevalence of use of medications with potential for fetal harm (% of women), most commonly used medications.
Blotière et al. (2021) [34]	France 2016-2017	Nationwide study based on the French health databases, medication use based on prescription fills.	1 844 447	Swedish, Australian	FASS category D: 2.2%, doxycycline, erythromycin, ondansetron. Australian category D/X: 3.9%, doxycycline, nicotine, fluconazole.
Ahmed et al. (2020) [37]	Ethiopia 2017	Cross-sectional study, information on medication use collected via interviews.	1117	FDA, Australian	FDA C, D, X and Australian B3, C, D, X: 13.6%, diclofenac, ibuprofen, omeprazole.
Raichand et al. (2020) [35]	Australia 2005-2012	Study based on population-based datasets including dispensing records.	191 588	Australian	Category D/X: 2.0%, doxycycline, paroxetine, valproate.
Donald et al. (2020) [38]	New Zealand 2005-2015	Cohort study linked to national dispensing database.	874 884	Australian	Category D: 4.3%, nicotine, paroxetine, doxycycline. Category X: 0.035%, isotretionin, misoprostol, leflunomide.
Zhang et al. (2019) [39]	China 2015	Study based on a national health insurance database (CHIRA), including information on use of prescription medications.	11 373	FDA	Category D: 5.0%, diazepam, alprazolam, phenobarbital. Category X: 7.5%, oxytocin, misoprostol, ribavirin.
Rouamba et al. (2018) [40]	Burkina Faso 2016	Cohort study, self-reported medication use.	2371	FDA, Australian	FDA C, D, X and Australian B3, C, D, X: 39%, quinine, tetanus vaccine, amodiaquine.
Zomerdijk et al. (2015) [41]	The Netherlands 1999-2007	Population based cohort study, medications from prescription database.	203 962	Swedish, Australian, FDA	FASS D/Australian or FDA D and X category: 5.1%, doxycycline, paroxetine, progesterone.
Cleary et al. (2010) [42]	Ireland 2000-2007	Cohort study, maternal report of medications in interview.	61 252	FDA	Category D: 2.5%, methadone, diazepam, paroxetine.

Author (year)	Country Study period	Design, exposure ascertainment	Sample size	Risk classification system	Main findings Prevalence of use of medications with potential for fetal harm (% of women), most commonly used medications.
					Category X: 3.2%, oral contraceptive, estradiol, flurazepam.
Kulaga et al. (2009) [43]	Canada 1998-2002	Cross-sectional study, prescription medications.	109 344	Briggs	6.3% filled a prescription for a medication with a potential for fetal harm. Benzodiazepines (lorazepam, clonazepam), fluconazole, doxycycline.
Gagne et al. (2008) [44]	Italy 2004	Retrospective study, based on health care database, prescription medications.	33 343	FDA	Category D: 2%, atenolol, carbamazepine, phenobarbital. Category X: 1%, simvastatin, atorvastatin, pravastatin.
Andrade et al. (2006) [45]	USA 1996-2000	Retrospective study based on automated databases of eight health maintenance organizations, prescription medications.	114 165	FDA	Category D/X: 5.8%, oral contraceptives, doxycycline, atenolol.
Riley et al. (2005) [46]	USA 2001-2003	Cohort study, prescription medications obtained from medical records.	1626	FDA	Category D/X: 4.0%, most commonly tetracycline, hormonal contraceptives, antidepressants (nortriptyline and amitriptyline).
Schirm et al. (2004) [47]	The Netherlands 1997-2001	Cross sectional study based on pharmacy records.	7500	Australian	Category D/X: 12% Prescriptions with a potential for fetal harm were mainly from ATC code N05, N06, M01A.
Malm et al. (2004) [48]	Finland 1999	Retrospective cohort study, based on prescription records.	43 470	Swedish, Australian, FDA	20.4% of women purchased at least one medication classified as potentially harmful; pivmecillinam, clomifene, ibuprofen and 3.4% purchased at least one medication classified as clearly harmful: follitropin α or β, doxycycline, estradiol.

FASS category, pregnancy risk category by the Swedish risk classification system; ATC, Anatomical Therapeutic Chemical Classification.

1.4 Analgesics in pregnancy

1.4.1 The need for analgesic pharmacotherapy

Pain may be experienced as a result of physiological changes associated with pregnancy or acute, non-obstetric causes. Common examples would be pelvic girdle pain, low back pain, muscular, and stomach pain. Prevalence estimates of pelvic girdle pain and low back pain range from 24% to 90% of pregnancies [49-51]. Other acute conditions could be related to surgery, injuries etc. Pain may also be related to pre-existing chronic conditions [52]. Examples of chronic pain conditions are migraine (affecting up to 20% of women of reproductive age [53]) and arthritis. Some illnesses may improve during the course of pregnancy, while others may exacerbate. For instance, worsening of headache and migraine often occur during the first weeks of pregnancy, whereas inflammatory conditions affecting the musculoskeletal system usually arise later in pregnancy [54]. The pain severity varies depending on the specific condition. Moreover, pain may indirectly affect pregnancy outcomes, as inadequately managed pain is associated with sleep deprivation, depression, and hypertension [55, 56]. Thus, the need for adequate pain management in pregnancy is necessary and analgesics may be used to manage or relieve pain [52].

1.4.2 Prevalence, patterns of use and treatment guidelines

Analgesics can be grouped as non-opioid analgesics and opioid-analgesics. Non-opioid analgesics include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and acetylsalicylic acid. Opioids are further categorized as weak (including codeine and tramadol) or strong (morphine, oxycodone) opioids [55]. Opioids used for treatment of opioid dependence and illicit opioids are outside the scope of this thesis.

The main indication for analgesics are pain management, however, some of them are also used for their anti-pyretic and anti-inflammatory properties. As a group, analgesics are used by 50 to 70% of pregnant women [3, 8]. In general, analgesics should be used at the lowest effective dose for the shortest possible duration. In addition, one should use single agents instead of combining analgesics to avoid “cocktail”-effects [52]. The different analgesics are described in more detail below.

Paracetamol is considered the first line analgesic in pregnancy. It is available as an over-the-counter medication and on prescription. It is widely used in all trimesters of pregnancy and prevalence estimates range from 40 to 65% of pregnancies [1, 3,

57]. In the study by Bandoli et al. [57] including 2441 participants from the MotherToBaby study (2004-2018), 1515 women (62%) were exposed to paracetamol during pregnancy. Among the paracetamol-exposed women, 40% reported use in only one trimester, and 30% reported use in two and three trimesters, respectively. The authors also characterized use with regard to days of use and among the exposed women, 58% reported less than 10 days of use, 13% reported between 10 and 19 days of use and 18% reported greater than 20 days of use during pregnancy [57]. Safety aspects of paracetamol use during pregnancy will be discussed in section 1.5.

NSAIDs are used by 5 to 15% of pregnant women [3, 58] and the use generally declines throughout pregnancy [59]. Common NSAIDs include ibuprofen, diclofenac and naproxen. Ibuprofen is the analgesic of choice second to paracetamol [60]. NSAIDs are available over-the-counter and on prescription in Norway. NSAIDs do not seem to increase the risk of malformations [60]. Use around conception has been associated with an increased risk of miscarriage [60]. Hence, NSAIDs can be used in the first and second trimester of pregnancy [61]. NSAIDs should be avoided in the last part of pregnancy due to increased risk of premature closure of the ductus arteriosus and because they can result in low levels of amniotic fluid [60, 62]. FDA recommends to avoid use of NSAIDs after week 20 of pregnancy [62].

Acetylsalicylic acid is used to treat mild pain and fever, and estimates of use is <10% [1]. However, it is not considered an analgesic medication of first choice [60]. When used in analgesic doses (500 mg), acetylsalicylic acid confers the same risks as NSAIDs when used in late pregnancy. Hence, acetylsalicylic acid should be avoided in the third trimester [60, 63].

Opioid analgesics are used in moderate to severe pain management. Opioid analgesics are available on prescription and are used by 3 to 28% of pregnancies. Prevalence estimates are in the lower range in Scandinavian countries, whereas the prevalence of use is higher in the U.S. [33, 64-67]. In the study by Engeland et al [33], based on prescriptions dispensed from the Norwegian Prescription database (2005-2015) and including 638 532 pregnancies, 1.4%, 1.0% and 1.1% were dispensed an opioid analgesic in the first, second, and third trimester, respectively. Straub et al. [68] used group-based trajectory models to look at patterns of dose, duration, and timing of prenatal prescription opioid exposure. In a cohort of 18 869 pre-pregnancy chronic opioid users within the 2000-2014 Medicaid Analytic eXtract, Straub et al. identified 6 different trajectory patterns during the course of pregnancy (continuous very low-dose use, continuous low-dose use, initial moderate

dose with a gradual decrease to very low dose use, initial high dose use with a gradual decrease to very low dose use, continuous moderate dose use, and continuous high-dose use). Recently, there has been an increased use of opioids in the general population and this may also affect women of childbearing age [69]. If opioids are used over a longer period, they may cause tolerance and dependence. A study from Sweden showed that among pregnant women who filled opioid analgesic prescriptions there has been a large increase in strong opioid analgesic prescriptions, from 6.1% in 2007 to 17.1% in 2013 [66]. U.S. guidelines recommend no or minimal use of opioids for chronic pain if possible [70]. Norwegian guidelines additionally recommend that opioids should be avoided in the last part of pregnancy due to risks of neonatal withdrawal symptoms [71]. Safety aspects of analgesic opioid use during pregnancy will be discussed in section 1.6.

Knowledge about the safety of analgesics in pregnancy is fundamental to making informed and evidence based decisions when treating women with pain during pregnancy. Little is known about the long-term effects of prenatal exposure to analgesics. Concerns have been raised regarding a potential adverse effect of prenatal exposure to paracetamol and opioid analgesics on fetal neurodevelopment [72, 73]. Neurodevelopmental outcomes after prenatal exposure to medications have been highlighted in calls for research action from European and American consortia on medication safety in pregnancy [12, 14]. Given the widespread use of paracetamol and opioid analgesics, a potential adverse effect could have huge implications for public health. Previous studies examining associations between prenatal exposure to paracetamol and neurodevelopmental outcomes in children have methodological limitations that limit inference and the results are inconclusive [74, 75]. Few studies have investigated the association between prenatal exposure to opioid analgesics and neurodevelopmental outcomes in children [76]. Thus, more studies are needed.

1.5 Safety aspects of paracetamol in pregnancy

Paracetamol is widely used in pregnancy due to its favorable safety profile [77]. Paracetamol use has not been considered to be associated with increased risks of malformations, preterm birth, or other immediate birth outcomes [77, 78]. However, some studies have reported increased prevalence of malformations of the male genitals among exposed [59, 77, 79]. In the study by Jensen et al. [79], prenatal exposure to paracetamol for more than 4 weeks in the first and second trimester was

associated with an increased risk of cryptorchidism (Hazard Ratio (HR): 1.38, 95% Confidence Interval (CI): 1.05, 1.83).

1.5.1 Neurodevelopment in the offspring

Paracetamol crosses the placenta and the blood-brain-barrier [80]. Several biologically plausible mechanisms have been suggested for interfering with normal brain development. This includes neurotoxicity induced by oxidative stress [81, 82], interaction with maternal hormones important for normal brain development [83], and stimulation of endocannabinoid receptors required for normal axonal growth and fasciculation [84].

Within the last decade, several studies have suggested a link between paracetamol exposure during pregnancy and adverse neurodevelopmental outcomes in children, in particular attention-deficit/hyperactivity disorder (ADHD) [74]. In 2013, Brandlistuen et al. [72] published a study that reported that long-term exposure to paracetamol during pregnancy (>28 days) was associated with poorer gross motor development, communication, externalizing, and internalizing behavior in 3-year-old children. This study received much media publicity and was debated in the scientific community [85, 86]. The following year, Liew et al. [87] suggested that prenatal exposure to paracetamol was associated with higher risk of hyperkinetic disorder and ADHD-like behaviors in children aged 7 years. Since then, several studies have been published finding positive associations between prenatal paracetamol exposure and autism spectrum disorder [88-90], language [91], and cognitive and behavioral outcomes [92-98]. Findings from observational studies are illustrated in Figure 1.1 and presented in detail in Table A.1

A recent meta-analysis of six European cohort studies including 73 881 mother-child pairs, indicated that children prenatally exposed to paracetamol were 19% more likely to have autism spectrum conditions (Odds Ratio (OR): 1.19, 95% CI: 1.07, 1.33) and 21% more likely to have ADHD symptoms (OR: 1.21, 95% CI: 1.07, 1.36) compared to unexposed children, respectively [99]. Paracetamol exposure was assessed through maternal report and outcomes were assessed in children between 4-12 years using validated instruments [99]. An overview of meta-analysis on the association between prenatal exposure to paracetamol and neurodevelopmental outcomes in children is given in Table A.2.

Given the widespread use of paracetamol during pregnancy, a potential adverse effect on child neurodevelopment would be a public health concern. Due to the growing body of evidence signaling modest associations between prenatal exposure

to paracetamol and adverse neurodevelopmental outcomes, it is important to understand whether these associations are causal. The existing literature may be limited by potential confounding, including by indication, by unmeasured factors and bias introduced by exposure and outcome misclassification, as well as study participant loss to follow-up [100]. This has been highlighted in several articles [74, 75, 100-102]. In brief, paracetamol is used for a wide range of reasons, thus making the collection of indications of each use difficult. Paracetamol is available over-the-counter and exposure ascertainment in observational studies rely on maternal self-report, which is influenced by the accuracy of recall. Under-reporting due to flawed recall should be expected [74]. In addition, unmeasured confounding (e.g. by genetics) poses important challenges as we do not know the magnitude or direction of bias and cannot account for it fully [103, 104].

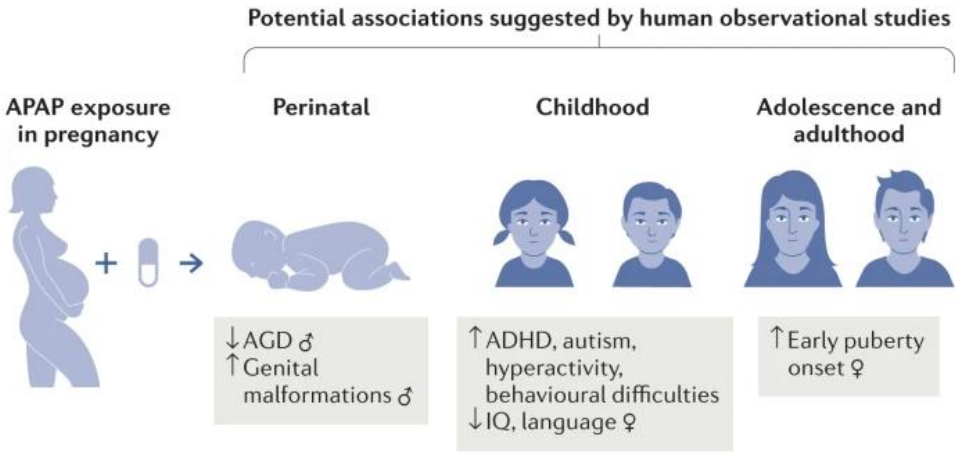


Figure 1.1 Summary of findings related to prenatal exposure to paracetamol and outcomes from observational studies.

Figure obtained from Bauer et al. 2021 [96]. AGD, anogenital distance; APAP, *N*-acetyl-*p*-aminophenol.

Several regulatory agencies have made statements regarding the evidence supporting associations between prenatal paracetamol exposure and neurodevelopmental outcomes. In brief, FDA announced in 2015 that the evidence supporting associations between analgesics and ADHD in children was too limited to draw any conclusions [105]. This was followed by a similar statement from the Society for Maternal-Fetal Medicine, stating that paracetamol is still safe to use during pregnancy [106]. This was further supported by a statement from the European Medicines Agency, based on recommendations from the Pharmacovigilance Risk Assessment Committee, which emphasized the inconclusive nature of the evidence in the literature [107]. During the fall of 2021,

a new consensus report by experts was published that calls for precautionary action regarding paracetamol use in pregnancy [108].

1.6 Safety aspects of opioid analgesics in pregnancy

Opioids are medications acting in the central nervous system, available on prescription, and primarily used for treatment of pain [109]. In addition, certain opioids are used in the context of opioid maintenance therapy (methadone and buprenorphine). It is important to distinguish between women that use opioids for opioid maintenance therapy and women that use opioids for pain management. There are differences in sociodemographic characteristics and lifestyle factors that limit the generalizability of findings between those two populations [110]. Previous research assessing the safety of opioids in pregnancy have mainly been conducted with women that used opioids for opioid maintenance therapy or for illicit purposes.

With respect to immediate birth outcomes, studies have investigated the risk of malformations [111-113] and other adverse birth outcomes [110, 114]; however, the results are mixed. In the study by Broussard et al. [111] they found an increased risk of congenital heart defects (OR: 1.40, 95% CI: 1.10, 1.70) after first trimester exposure to opioid analgesics. Nezvalová-Henriksen et al. [113] did not find increased risks of major malformations in children prenatally exposed to codeine in the first trimester when compared to unexposed (OR: 0.80, 95% CI: 0.50, 1.10). Two recent studies [115, 116] found small increased risks of preterm birth after any exposure during pregnancy. However, the study by Sujan et al. [116] found that the overall estimate of preterm birth (OR: 1.38, 95% CI: 1.31, 1.45) was largely attenuated in sensitivity analysis. They consequently concluded that the findings were largely due to unmeasured confounding factors. High consumption or long-term treatment in the last part of pregnancy is associated with neonatal withdrawal syndrome [117], but other exposure patterns may also be associated with increased risks [68]. If opioids are given in connection with childbirth, there is a risk of respiratory depression in the newborn [117].

1.6.1 Neurodevelopment in the offspring

Opioids cross the placenta and the blood-brain-barrier [80]. Animal research has shown that prenatal exposure to opioids alters brain structures and functions; thus, opioids might interfere with fetal neurodevelopment [118-120]. In recent years and in connection with the opioid epidemic, there has been a growing concern about the potential impact of prenatal opioid exposure on child neurodevelopment [12, 121].

However, the literature regarding neurodevelopmental consequences after prenatal exposure to opioid analgesics is limited [76]. In a systematic review by Hjorth et al. published in 2019 [76], only two studies were identified [73, 122]. Since then, some other studies have been published [67, 123, 124]. Table 1.3 presents an overview of studies examining the association between prenatal exposure to opioid analgesics and neurodevelopmental outcomes in children. Two studies were based on a large Norwegian birth cohort [122, 124] and reported that prenatal analgesic opioid exposure was not associated with impaired language competence or communication skills in preschool children. The study published by Wen et al. [67] reported that prenatal exposures for >14 days or exposures to high cumulative opioid doses increased the risk of neurodevelopmental disorders (HR range: 1.22-1.70), compared to no exposure.

The current literature is sparse and have investigated few domains within the realm of neurodevelopment. Most of the studies have assessed outcomes in pre-school aged children or younger, but studies with longer follow-up are also needed. Effects may be subtle and may not become evident until more complex cognitive tasks are demanded. Some studies have explored associations of timing [73] and/or duration of exposure [67, 124], whereas others have not [123]. Since opioids are used in the management of moderate to severe pain, confounding by indication is an important concern and need to be carefully addressed. Skovlund et al. [124] and Wen et al [67], have taken maternal pain conditions into account, although different methods were utilized. Overall, more studies are needed to further the understanding of the safety of prenatal exposure to opioid analgesics on offspring neurodevelopment.

Table 1.3 Studies examining the association between prenatal exposure to opioid analgesics and neurodevelopmental outcomes in children.

Author (year)	**Design** **Study period** **Country**	**Method to account for confounding**	**Sample size**	**Exposure** Classification, Ascertainment, Number of exposed,	**Outcome**	**Main findings**
Wen et al. (2021) [67]	Retrospective cohort study 2010-2012 USA	Propensity score with fine stratification, demographic characteristics, obstetric characteristics, maternal comorbid mental and pain conditions, measures of burden of illness.	24 910	Opioid prescription during pregnancy (yes/no). Cumulative exposure: Dose; high or low. Duration; ≥14 days 1899 (7.6%)	Presence of one or more of the following: intellectual disorders, communication disorders, ASD, ADHD, specific learning disorder, motor disorder, other neurodevelopmental disorders based on ICD-9/10 codes in medical claims.	Mean age at diagnosis was 2.5 years. No association between fetal opioid exposure and the risk of neurodevelopmental disorders (HR: 1.10, 95% CI: 0.92, 1.32). Increased risk of neurodevelopmental disorders were observed in children with longer cumulative exposure duration (HR: 1.70, 95% CI: 1.05, 2.96) or high cumulative opioid doses (HR: 1.22, 95% CI: 1.01, 1.54).
Skovlund et al. (2020) [124]	Birth cohort study 1999-2008 Norway	Adjustment for paracetamol, any pain, chronic disease, planned pregnancy, smoking, parental education, work situation, maternal and paternal age, parity, marital status, BMI, alcohol, anxiety and depression, co-medications, illegal drugs.	33 407	Main analysis: yes/no. Did explore other exposure classifications. Maternal self-report 584 (1.7%).	Language and communication development in 5-year olds, measured by validated instruments (ASQ, SLAS, Language20Q), parent reported.	No associations between opioid use and lower language competence or communication skills were found.
Azuine et al. (2019) [123]	Cohort study 1998-2014 USA	Adjustment for maternal age, household income, race, marital status, maternal	8509	Maternal self-reported opioid use and/or clinical diagnosis of NAS.	Neurodevelopmental disabilities from EMR. ADHD, conduct disorder based on ICD-codes.	For children ≤6 years, exposed children had higher odds of conduct disorder (OR: 2.13, 95% CI: 1.20, 3.77) and lack of expected normal

Author (year)	**Design Study period Country**	**Method to account for confounding**	**Sample size**	**Exposure** Classification, Ascertainment, Number of exposed,	**Outcome**	**Main findings**
		education, preterm birth, low-birth-weight.		Exposure ascertained by interview and presence of NAS from medical records. Yes/no exposure.		physiological development (OR: 1.80, 95% CI: 1.17, 2.79) compared to unexposed. For children ≥6 years, exposed children had increased risk of ADHD compared to unexposed (OR: 2.55, 95% CI: 1.42, 4.57).
Rubenstein et al. (2019) [73]	Multi-site case-control study 2003-2012 USA	Adjustment for maternal education, race, smoking during pregnancy, psychiatric conditions prior to childbirth, and study period.	2946	Maternal prescriptions abstracted from medical records, Any exposure during peri-pregnancy, by trimesters. 336 (7.7%).	ASD, developmental delay/disorder (DD) with no ASD features, ASD/DD with autism features.	Preconception opioid prescription was associated with ASD (OR: 2.43, 95% CI: 0.99, 6.02) and ASD/ DD with autism features (OR: 2.64, 95% CI: 1.10, 6.31) compared to mothers without prescriptions. Odds for ASD and ASD/DD were non-significantly elevated for first trimester prescriptions.
Skovlund et al. (2017) [122]	Birth cohort study 1999-2008 Norway	Adjustment for maternal work situation, paternal education, maternal BMI, parity, smoking, use of benzodiazepines or SSRI, maternal health.	51 679	None, one period, two or three periods, maternal self-report 892 (1.2%).	Language competence and communication skills in 3-year olds, measured by validated instruments, parent reported.	No association between opioid use and reduced language competence (OR: 1.04, 95% CI: 0.89, 1.22) or communication skills (OR: 1.10, 95% CI: 0.95, 1.27) was found.

ASQ, Ages and Stages Questionnaire; SLAS, The Speech and Language Assessment Scale; Language20Q, The Twenty Statements about Language-Related Difficulties list; CPRS, Conners Parent Rating Scale; NAS, Neonatal abstinence syndrome; ASD, Autism spectrum disorder.

1.7 Perinatal pharmacoepidemiology

Pharmacoepidemiology can be defined as ”the study of the use of and the effects of drugs in large numbers of people” and is a research field bridging between clinical pharmacology and epidemiology [125]. In other words, it applies epidemiological methods in studies of the use and effects of medications at a population level [125]. One distinguishes between descriptive and analytical pharmacoepidemiology, the first is primarily concerned with medication utilization, patterns of use and factors associated with such use. The latter, analytical pharmacoepidemiolgy, aims at determining measures of associations between exposures and outcomes [125].

The sections to follow will introduce concepts in pharmacoepidemiology relevant in the context of pregnancy research and this thesis. This includes description of study designs, data sources, and methodologic challenges when studying medication use and safety in pregnancy. The final section will deal with the challenge of interpreting associations obtained from observational studies.

1.7.1 Study designs

Randomized controlled trials are considered the “gold standard” in assessing exposure effects and safety [126, 127]. Ethical reasons limit the inclusion of pregnant women in clinical trials [6, 128]. Thus, pregnancy research is mainly based on large observational studies, including studies with a cohort or case-control design, to investigate the effect of medication exposure on immediate or long-term outcomes [6].

Cohort studies have a prospective design and have the advantage of collecting information about exposures before the outcomes are recognized [15]. This approach involves identification of a population to be followed-up over a longer period and periodically collecting information on sociodemographic variables, exposures, and potential confounders [15]. Participants may enter the study at different time points [129]. An advantage is that information on rare exposures can be collected and examined on several different outcomes [130]. Cohort studies are however expensive and may suffer from loss to follow-up or participant drop out. Low participation rates may also introduce selection bias [131]. Further, there may exist differences in estimates of prevalence between exposure and outcome between those who participate and non-study participants, which may lead to biased exposure-outcome associations [132]. Examples of cohort studies include the birth cohorts established in Denmark [133] and Norway [134].

Case-control studies offer an advantageous study design when studying rare outcomes, for example the cause of specific birth defects [15]. Individuals are included based on the outcome status. Cases are defined as those with the outcome, whereas controls are defined as those without the outcome under study. Exposure status is collected retrospectively and exposure history is then defined as exposed or unexposed. Retrospective exposure collection may introduce recall bias if a mother of a child with a malformation recall their exposures in different ways than do mothers of healthy children [135]. This draws attention to the question of selecting appropriate controls. It has been suggested to use a malformed control group in order to reduce the opportunity for differential recall of exposure between mothers of cases and controls [15, 136]. This is supported by the fact that a teratogen seldom increases the risk equally for all malformations [137]. An example of a case-control study is the National Birth Defects Prevention Study in the U.S. [138].

Another design used in pharmacoepidemiology is cross-sectional studies, which provide a snapshot of the population with respect to disease or exposure status at a specific point in time [139]. Information about exposures and diseases are collected simultaneously. Cross-sectional designs may be used in studies of medication utilization [3].

1.7.2 Data sources

There are many data sources available for pharmacoepidemiological research. Choosing a data source depends on the research question at hand and the resources available [131]. The sources often rely on collection of primary (self-reported in surveys) or secondary data (retrieved from registries or automated databases) [15]. Studies of medication safety in pregnancy are often based on linkage of several data sources [140]. This because linkage of various data sources may offer advantages over “single database” research, including complimentary information on variables, and availability of more confounder, exposure and outcome variables [140]. The Nordic countries presents a unique opportunity because each citizen is given a unique personal identification number which enables linkage of individual, personal information across different data sources.

Surveys collect data via interviews or questionnaires, and may vary greatly in size [141]. Questionnaires may be paper-based or electronically administered, and information is often self-reported by the participants [131]. Within the last decade, there has been a growing interest in the utilization of e-epidemiology [142]. Since women use the Internet to a very high extent during pregnancy to search for pregnancy-related information [143], this population is a suitable target group in e-

epidemiology. There are validation studies that indicate that the quality of data obtained with web-based questionnaires is sufficient [144]. For instance, van Gelder et al. [145, 146] have undertaken a series of validation studies within the PRIDE study on a number of key exposures and outcomes relevant for pregnancy research.

Registries are data collection programs that collect data for a specific purpose to assess a certain exposure or outcome. Examples include birth registries [147, 148] and in those registries, report is often mandatory and information is filled in by healthcare professional [147].

Automated databases include both administrative and non-administrative databases. Administrative databases include information on, for example, dispensed and prescribed exposure at the pharmacy, medical diagnosis in out-patient clinics or hospitals, or payment/reimbursement connected to a medical service [140]. Electronic health medical records represent a non-administrative database and include information that is collected routinely by a general practitioner. Medical record databases are often rich on maternal characteristics, health and medication exposures, in addition to pregnancy outcomes [140, 149].

1.7.3 Methodologic considerations

1.7.3.1 Exposed or not exposed?

Information about medication use during pregnancy can be derived from self-report among pregnant women or from registries and claims databases [6]. Registries and databases capture prescribed or dispensed medications, whereas self-report may also include medications available over-the-counter. All sources have strengths and weaknesses in this regard [128, 150]. It has been shown that there is good agreement between self-report and prescription data for prescribed medication used chronically and substantially less for medication used episodically [150, 151]. Use of medication available both with and without a prescription is not well reflected in prescription records alone [150].

Regarding the exposures in this thesis, paracetamol exposure assessment have primarily relied on maternal self-report (Table A.1). Maternal self-report is influenced by the accuracy of recall [150]. A concern with the previous literature is related to exposure misclassification. Paracetamol is an intermittently used medication and taken for a wide range of reasons [57]. Paracetamol may be confused with other medications and with respect to timing of use [100]. Consequently, some degree of misclassification is inevitable. Timely collection of exposure information would probably minimize such exposure misclassification and recall bias [108]. In

studies where information on exposure is collected prior to outcome measurement, misclassification of exposure is likely to be non-differential. Non-differential misclassification generally moves estimates towards the null [100].

With respect to opioid analgesics, exposure status have been ascertained by self-report and prescription records (Table 1.3). Not all prescribed and dispensed medications are actually taken [152]. Pregnant women may deliberately discontinue medications upon learning of conception or prior to exhausting its supply. Old prescriptions may also be used during pregnancy, particularly for medications used as needed [128]. This may lead to misclassification of exposure status. Prescription registries gather information prospectively and independent of the outcome and any misclassification can be assumed to be non-differential. Opioid analgesics are intermittently used medications, and self-report may be limited by the accuracy of recall [150].

There exists methods to evaluate the impact of exposure misclassification on risk estimates, such as probabilistic bias analysis [153].

Furthermore, it is important to consider how exposure to a medication is classified. In many studies, exposure to a medication is classified as “ever exposed” versus “never exposed” during pregnancy [154]. This categorization does not reflect real-world exposure patterns and does not distinguish between a single dose and long-term use. Moreover, this binary approach does not take into account important aspects such as dosage and timing of exposure [154]. These aspects are important when addressing causation in medication safety in pregnancy research, as discussed in section 1.7.4 below.

1.7.3.2 Outcome ascertainment

In recent years, there has been increased attention to long-term consequences following prenatal exposures to medications and particularly neurodevelopmental outcomes in childhood [7], which is a focus of this thesis. The term “neurodevelopment” encompasses a broad spectrum of outcomes [155], including cognition and intelligence, psychiatric diagnosis, behavioral problems, communication skills and emotional regulation. It has been debated how neurodevelopment should be measured and what outcomes should be assessed [76, 156, 157]. Some studies have used medical diagnosis, whereas other have used psychometric instruments assessed by parents, teachers or healthcare professionals [76]. There are concerns regarding whether medical diagnosis are sensitive enough to capture subtle effects in neurodevelopment and the clinical relevance of parent-reported outcomes has been questioned [85]. Moreover, in 2019, Hjorth et al.

published a set of recommendations when conducting studies investigating neurodevelopmental safety of prenatal medication exposures [76]. These recommendations include:

- Investigating a wide variety of outcomes in order to establish neurodevelopmental safety.
- Previous literature should inform choice of outcomes to be measured.
- The outcome measure should be relevant for the child's age.
- Information regarding reliability and validity of the outcome measure should be reported.
- Data sources should complement each other.

Furthermore, misclassification of outcome is possible and may be differential if exposed children are monitored more closely than unexposed children because of suspicion of medication-induced effects [15].

1.7.3.3 Confounding

Confounding is a central issue in pharmacoepidemiological studies on medication safety in pregnancy. A simple definition of confounding is the confusion of effects [158]. A confounder is a factor that is associated with both the exposure and the outcome, and that does not lie on the causal pathway between exposure and outcome [158]. This can be illustrated graphically with the aid of a directed acyclic graph (DAG) [159]. A simple example is presented in Figure 1.2, also including other relevant terms in this regard such as intermediates and colliders.

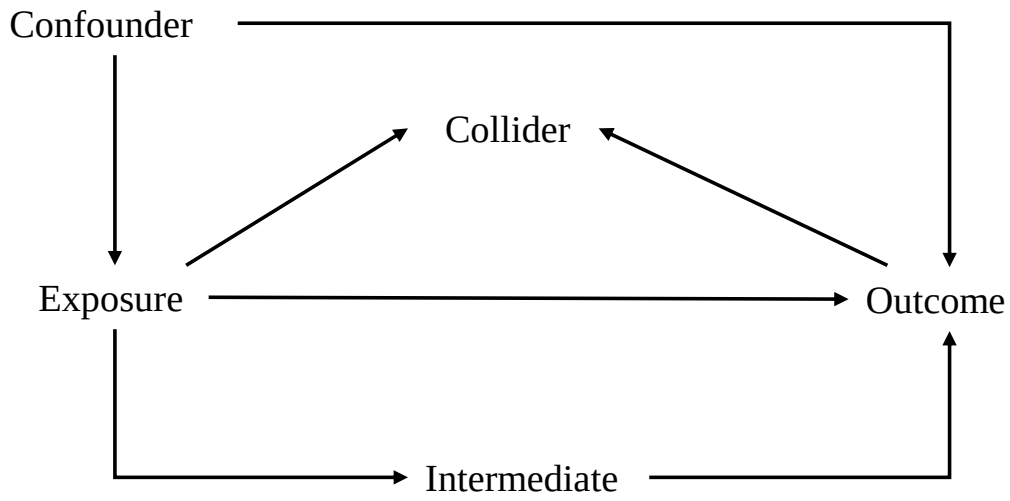


Figure 1.2 An example of a directed acyclic graph (DAG).

In a RCT, participants are randomly assigned to the exposure group or the unexposed group, and the distribution of background characteristics is assumed equal between groups [139]. This is not the case in an observational study. Those taking a medication may have background characteristics that differ systematically from those not taking a medication [160]. For instance, the indication for medication use will be more prevalent among medication users [161]. This may introduce confounding by indication if the indication for medication use is also associated with the outcome. Moreover, differences in sociodemographic variables such as age, smoking status and use of alcohol may differ between groups. These characteristics needs to be accounted for in the analyses in order to obtain valid effect estimates [159]. One should adjust for confounding factors, but it is not appropriate to adjust for intermediates or colliders [162]. To make these relationships explicit, one could utilize DAGs [163].

The amount of information on background characteristics available may vary depending on the data source. Some may be measured, while others remain unmeasured (such as genetic factors, family environment or personality traits) [104]. Epidemiological methods for dealing with measured confounding include the use of propensity scores [164, 165]. Propensity scores are a summary score that estimates the probability of treatment conditional on measured characteristics [166].

In order to account for unmeasured confounding, one may utilize methods such as sibling design, instrumental variables or active comparators [160]. The role of unmeasured confounding has been highly discussed in connection with prenatal paracetamol exposure and neurodevelopmental outcomes in children [100]. For instance, Brandlistuen et al. [72] and Gustavson et al. [167] applied sibling design in order to account for familial and genetic confounding. Several methods exist to examine the role of unmeasured confounding, including negative controls [168], calculation of the e-value [169] and probabilistic sensitivity analysis [170], and some will be utilized in this thesis.

A newer approach, when analyzing observational data, have been advocated by Hernàn and Robin [126, 171]. This is called the Target Trial. Here, observational data is used to emulate a randomized trial design [172]. However, there are certain conditions that must be met if an observational study is to be treated as a randomized experiment [171]. These conditions include the following:

- Consistency
- Exchangeability
- Positivity

In brief, these conditions imply that there should be a well-defined difference between exposed and unexposed so that the exposure should be possible to make into an intervention, there should be no unmeasured confounding and that every subject should have a positive probability of being exposed [171].

1.7.3.4 Missing data

Perinatal pharmacoepidemiological studies often encounter issues with missing data [173]. For instance, data from surveys may be missing due to drop-out of the study or because of non-response to one or several items [174, 175]. A frequently used approach to deal with this has been to perform a complete case analysis, in which the study sample is restricted to those without missing information in the relevant variables [173]. However, exclusion of participants may lead to reduced power in the analysis [175].

Another method for dealing with missing data is multiple imputation, in which missing information is filled in based on observed variables [175, 176]. Before applying this method, one should explore the extent and patterns of missing data in order to get a hint of the underlying mechanisms of missingness [173].

Data may be classified as missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) [175]. Data is considered to be MCAR when missingness is independent of observed and unobserved variables. This implies that there is no systematic differences between the missing and the observed variables [175]. If a participant inadvertently skip responses, data may be MCAR. MAR occurs if there is systematic differences between the missing values and the observed values, which can be explained by the observed data [175, 177]. An example could be that women with depression may be less likely to report smoking than non-depressed women. MNAR occurs when missing data depends on unobserved variables [175]. For example, women who smoke during pregnancy are less likely to report their smoking status.

Missing data in pharmacoepidmiological studies may introduce bias, depending on the reasons why data are missing and how missingness is handled [175]. Complete case analysis gives unbiased estimates when the missing entries of the excluded participants occur randomly (MCAR). The frequently used approach of multiple imputation by chained equations assumes MAR, which is a weaker assumption than MCAR and more likely to hold in observational studies. By including a variety of different variables in the imputation model, the MAR assumption is likely to be plausible, resulting in unbiased estimates. However, the MAR and MNAR assumption is not testable in practice, which makes it impossible to distinguish

between MAR and MNAR using observational data. Multiple imputation may lead to biased estimates when data are MNAR [175].

1.7.4 Addressing causation in pregnancy studies

Analytic observational pharmacoepidemiogical studies in pregnancy aims at determining measures of association between exposures and outcomes [125]. However, an observed association does not imply causation [178]. Several suggestions have been made in order to distinguish between causal and non-causal effects [179]. One of the most famous set of considerations or criteria was proposed by Bradford Hill in 1965 [180]. These criteria include the following:

- Strength
- Consistency
- Analogy
- Temporality
- Biologic gradient
- Plausibility
- Coherence
- Experiment
- Specificity

These viewpoints underwent various interpretations and applications in various fields, including teratology. In fact, Dr. Shepard adapted some of the Hill's viewpoints as criteria of proof of teratogenicity [181].

Special attention should be given to the temporality and plausibility criterion. The temporality criterion implies that the cause should occur before the effect, while the plausibility criterion implies that the exposure should have a biologic plausible mechanism for the effect [180]. Indeed, in pregnancy research exposure should occur at a critical point in fetal development. Figure 1.3 illustrates the vulnerable periods for development of various organ systems in the fetus. For instance, in studies investigating the risk of malformations, the exposure must take place in the first trimester (when the organs are formed), in order to potentially cause malformations [182]. However, in studies examining offspring neurodevelopment, the whole pregnancy period represents a vulnerable period [183]. In addition, the dose-response relationship (biologic gradient) is important to consider. Further, as the majority of pregnancy studies are observational the consistency criterion is also relevant meaning that study findings should be replicated across time, different sites and in different ways.

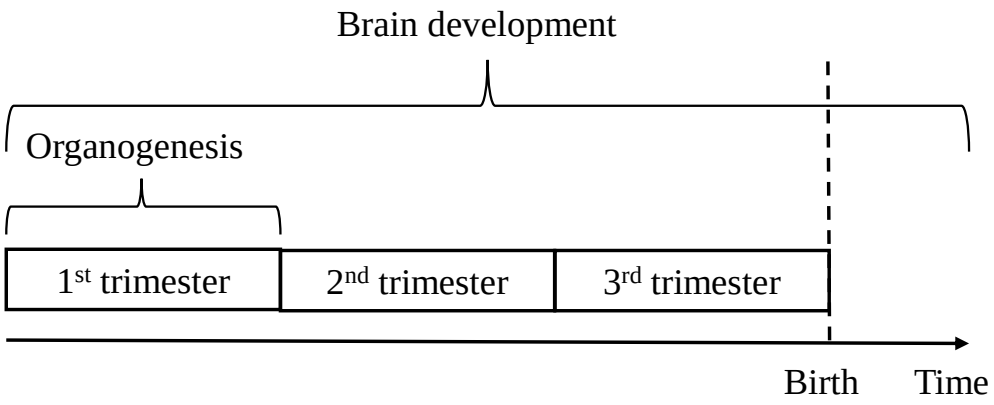


Figure 1.3 Illustration of important time periods during pregnancy for fetal development.

The foundation for most organs are formed in the first trimester, whereas the brain and central nervous system develops throughout pregnancy and continues into the first years of life.

2 Thesis aims

The overall aim of this thesis was two-fold. First, to explore the safety profile of medication used during pregnancy. Second, to extend our understanding of the safety of prenatal exposure to two commonly used analgesics (paracetamol and opioids), on offspring neurodevelopment. The specific aims of the four papers were as follows:

Paper I

To explore the safety profile of medication used during pregnancy.

To identify factors associated with use of potentially risky medication during pregnancy.

Paper II

To explore the association between prenatal exposure to paracetamol and communication skills, behavior and temperament in preschool-aged children.

Paper III

To examine the association between prenatal exposure to opioid analgesics and ADHD in children.

Paper IV

To investigate the association between prenatal exposure to opioid analgesics and scholastic skills in fifth grade.

3 Materials and methods

3.1 Data sources

The work in this thesis was based on data from different sources (Table 3.1) and the main methodological characteristics of the four papers are summarized in Table 3.2.

Table 3.1 Overview of data sources for papers I-IV.

	The Multinational Medication Use in Pregnancy Study	MoBa	MBRN	NorPD	NPR	SSB
Paper I	●					
Paper II		●	●			
Paper III		●	●	●	●	
Paper IV		●	●			●

MoBa, The Norwegian Mother, Father, and Child Cohort Study; MBRN, The Medical Birth Registry of Norway; NorPD, The Norwegian Prescription Database; NPR, The Norwegian Patient Register; SSB, Statistics Norway.

3.1.1 The Multinational Medication Use in Pregnancy Study

The Multinational Medication Use in Pregnancy Study was a cross-sectional, web-based study carried out between October 2011 and February 2012 [3]. The study included 9459 women from 18 countries: Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, the Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, the United Kingdom and the USA [3]. The study recruited pregnant women and mothers with a child less than one year of age through the placement of banners on national websites and/or social networks commonly visited by pregnant women and new mothers. The online questionnaire was available for a period of two months in each participating country. In the study by Lupattelli et al. [3], the representativeness of the study sample was compared on an individual country level with those of the potential general birthing or childbearing population in the same country. The study sample was found to be representative with respect to age, parity, and smoking habits. However, the sample comprised a group of women with higher education than the general birthing population in each country.

Table 3.2 Main aspects of the four papers included in this thesis.

Paper	Main data source(s)	Design	Setting / location	Study period	Study population	Specific inclusion criteria	Exposure	Other data source(s)	Outcome
I	The Multinational Medication Use in Pregnancy Study	Cross-sectional Medication utilization study	Multinational	October 2011-February 2012	Pregnant women and mothers with a child less than 1 year.	Living in European countries. Reporting of medication use during pregnancy.	All medications used during pregnancy.	-	Medication use according to safety profile.
II	MoBa MBRN	Population-based birth cohort	Norway	1999-2008 * Paper IV could not include MoBa children born 1999-2001 due to lack of consent.	Pregnant women from all over Norway, recruited in connection with their routine ultrasound examination in gestational week 17-18.	Live-born singletons, Q1, Q3 and Q4.	Paracetamol	-	Communication skills, behavior and temperamental problems.
III						Live-born singletons of mothers reporting an indication for opioid use, Q1, Q3.	Opioid analgesics	NPR, NorPD	ADHD diagnosis and symptoms.
IV							Opioid analgesics	SSB	Test scores from national tests in fifth grade.

MoBa, the Norwegian Mother, Father and Child Cohort Study; MBRN, The Medical Birth Registry of Norway; Q, questionnaire; NPR, Norwegian Patient Register; NorPD, the Norwegian Prescription Database; SSB, Statistics Norway; ADHD, attention-deficit/hyperactivity disorder.

3.1.2 The Norwegian Mother Father and Child Cohort Study

The Norwegian Mother, Father, and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [134]. Pregnant women from all over Norway were recruited between 1999 and 2008 through an invitation in connection with their routine ultrasonography examination in gestational week (GW) 17 or 18. The initial participation rate was 41% and the cohort now includes 114 500 children, 95 200 mothers and 75 200 fathers. Mothers were followed-up by paper-based questionnaires during pregnancy (in GW 17 [Q1] and 30 [Q3]) and after the child was born (at 6 months [Q4], 18 months [Q5], 3 years [Q6], 5 years [Q-5yrs] and onward. Follow-up is still ongoing. The MoBa study collected detailed information on a range of variables, including parental sociodemographic and lifestyle factors, maternal health, medication use, and child development. Compared to the general birthing population of Norway, participants were less likely to be young mothers, more likely to be married or cohabiting, and had a healthier lifestyle during pregnancy [132]. Templates of the MoBa questionnaires can be found at the website of the Norwegian Institute of Public Health [184].

3.1.3 The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) is a nationwide health registry containing information about all births in Norway [147]. Information about socio-demographic variables of the parents, maternal health before and during pregnancy, and any complications during pregnancy or birth is collected via standardized forms which are filled out by a midwife or other healthcare professionals [147].

3.1.4 The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) was established in 2008 and is a national health registry containing information on diagnosis and procedures from government-owned hospitals and outpatient-clinics, and all private health clinics that receive governmental reimbursement [185]. The diagnostic codes in the NPR follow the International Classification of Diseases, 10th revision (ICD-10).

3.1.5 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) was established in 2004 and collects data on all prescribed medications dispensed from pharmacies to patients [186]. The information from NorPD include the Anatomical Therapeutic Chemical

Classification System (ATC) code of individual medications dispensed, dispensing dates, and the amount dispensed.

3.1.6 Statistics Norway

Statistics Norway (SSB) is the main producer of official statistics in Norway and relies on data from official registers and other administrative data. SSB delivered data on parental education level, family income, and results of national tests, which were utilized in paper IV.

3.2 Study samples

Figure 3.1 presents simplified flowcharts for papers I-IV.

Paper I: We included pregnant women or mothers with a child less than one year of age, living in European countries. Further, women who did not report medication use during pregnancy and women who used unspecified medications were excluded. The use of iron, mineral supplements, vitamins, and herbal remedies was excluded from this analysis.

As shown in Table 3.2, papers II-IV were based on data from the MoBa and MBRN. Data were linked using the unique personal identification number given to all residents in Norway. Papers II-IV included MoBa participants with a MBRN record and their live-born singletons.

Paper II: We required participants to have completed MoBa Q1, Q3 and Q4. We excluded women with unspecified timing of paracetamol use and those who used combinatory paracetamol medications. Further, women with missing data on potential confounders and women lost to follow-up or with no outcome data at child age 5 years were excluded.

Papers III and IV: We restricted the sample to pregnant women who had returned MoBa Q1 and Q3. We excluded women with unknown timing of exposure to opioid analgesics and women who used opioids for opioid maintenance therapy. We further restricted the sample to include women with a possible indication for opioid analgesic use, i.e. women reporting a pain condition before and / or during pregnancy. In the secondary analysis of paper III, we excluded participants lost to follow-up or with no outcome data at child age 5 years. In paper IV, MoBa children born between 1999 and 2001 could not be included, due to lack of consent as they turned 18 before the end of follow-up. In addition, children with no outcome data on national tests in fifth grade were excluded.

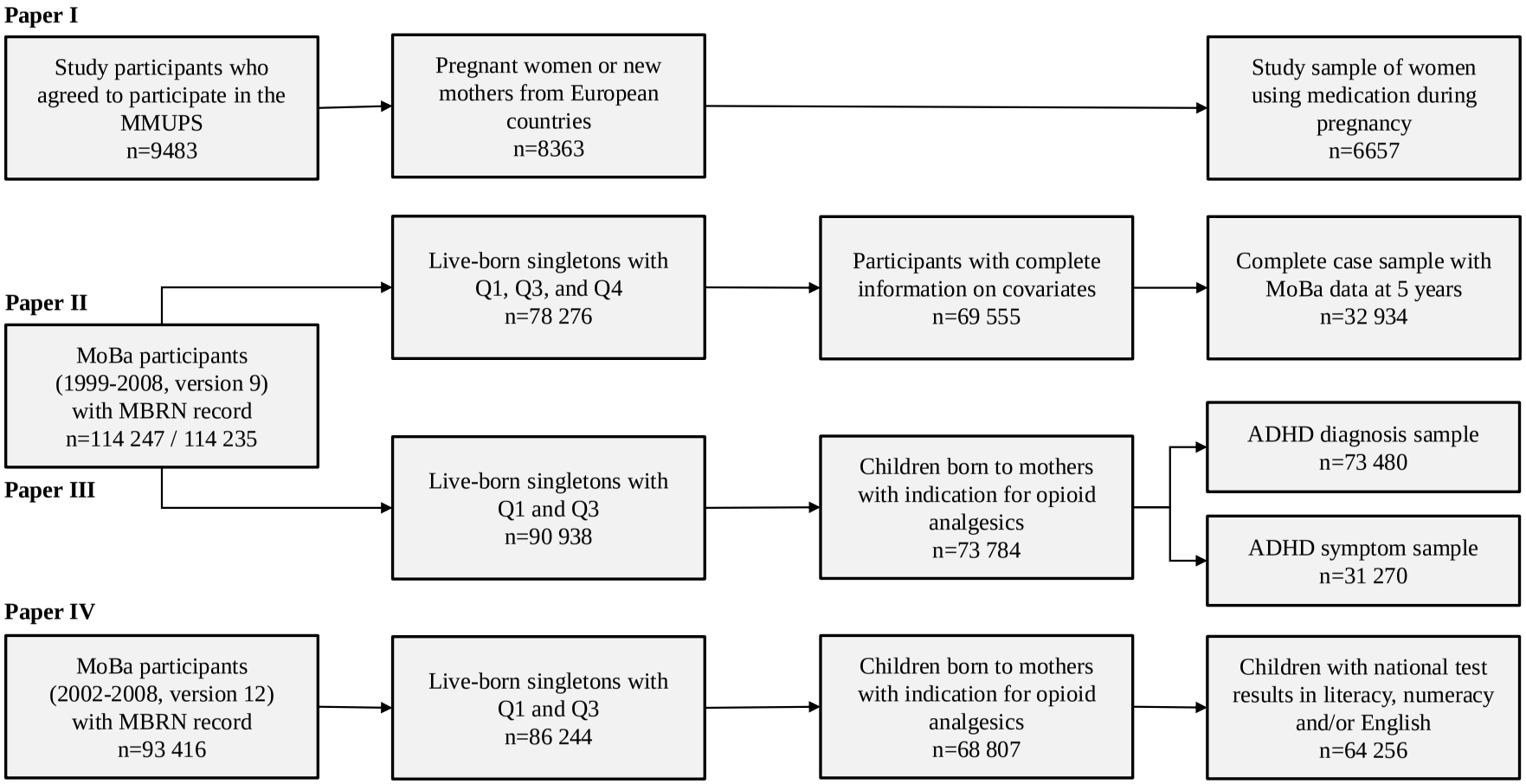


Figure 3.1 Simplified flowcharts to achieve the study populations in papers I-IV.

MMUPS, The Multinational Medication Use in Pregnancy Study; MoBa, The Norwegian Mother, Father, and Child Cohort Study; MBRN, The Norwegian Medical Birth Registry; Q, questionnaire; ADHD, attention-deficit/hyperactivity disorder.

3.3 Ethics

The Multinational Medication Use in Pregnancy Study was waived for ethical approval by the Regional Committee for Medical and Health Research Ethics (REK Sør-Øst). Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation (i.e., Italy, UK).

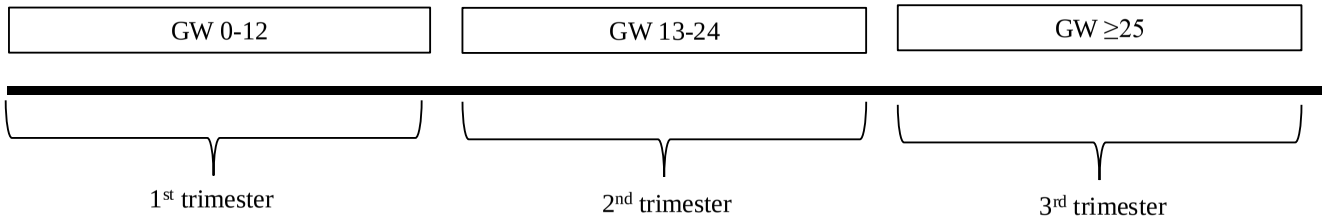
The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committee for Medical and Health Research Ethics. Currently, MoBa is based on regulations related to the Health Registry Act. All participants provided written, informed consent to participation and the use of their data from the Norwegian health registries. The papers II-IV were approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway; respective approval numbers were: 2015/2137 REK Sør-Øst, 2015/442/REK Sør-Øst, 2017/2205/REK Sør-Øst.

3.4 Measures

3.4.1 Medication use during pregnancy

Information about medication use during pregnancy was based on maternal self-report in all four papers, and included both over-the-counter and prescription medications. For paper I, information about medication use was retrieved from the Multinational Medication Use In Pregnancy Study, and for papers II-IV, information was retrieved from three MoBa questionnaires (Q1, Q3, and Q4). In both data sources, medication use was reported according to listed indications. More specifically, mothers were presented with a list of short- and long-term illnesses and asked to check the ones they had experienced. The Multinational Medication Use In Pregnancy Study included the most common short-term illnesses and the most prevalent chronic disorders, while the MoBa questionnaires have an extensive list of chronic, acute and pregnancy-related conditions in Q1, Q3, and Q4. For each checked item on the list, the mothers were asked to indicate any medications taken and specify the timing of use. Open-ended questions also allowed the women to report on any other medication use for non-specified conditions. The Multinational Medication Use In Pregnancy Study questionnaire also included five specific questions about the use of over-the-counter medications, with examples of branded product names in the various countries to enhance recall.

Paper I: Maternal report in the Multinational Medication Use in Pregnancy study



Papers II-IV: Maternal report in the MoBa

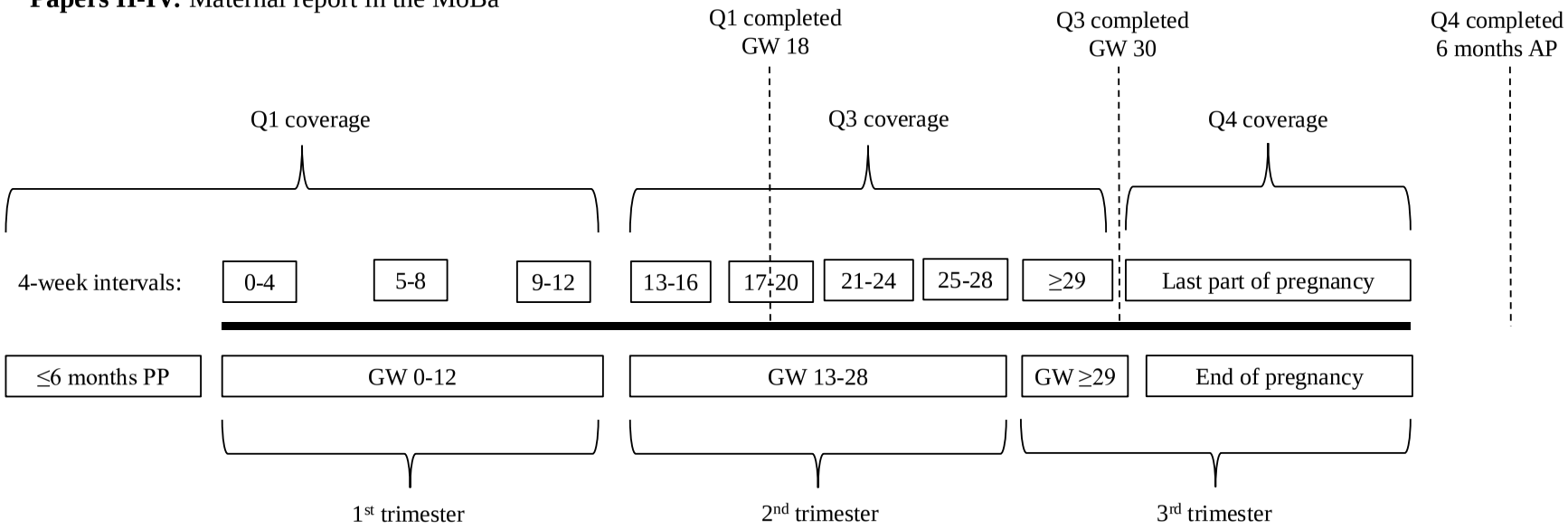


Figure 3.2 Exposure categorization.

GW, gestational week; PP, pre-pregnancy; AP, after pregnancy; Q, questionnaire.

We used the ATC system, by the World Health Organization [187], to classify medication use. For paper I, all medications were coded into the corresponding ATC fifth level. In paper II, women reporting use of paracetamol (ATC N02BE01) were considered as exposed, and in papers III and IV, women reporting use of opioid analgesics (ATC N02A) were considered exposed.

Exposure was reported according to trimesters in the Multinational Medication Use In Pregnancy Study (paper I), and according to four-week intervals (for example gestational week 5-8) in the MoBa study (papers II-IV) (Figure 3.2). In papers II-IV, we examined associations with both exposure timing and duration of exposure. Timing was categorized into trimesters. To investigate duration of exposure, we used number of trimesters (paper II) and number of 4-week intervals (papers III and IV) as proxies of duration. For a more detailed exposure classification, please refer to the respective papers.

3.4.2 Comparators

This section applies to papers II-IV. In paper II, children of mothers who used paracetamol during pregnancy were compared to children of mothers who did not use paracetamol during pregnancy. In papers III and IV, among all women reporting pain before and / or during pregnancy, we defined two comparator groups. Our main comparison was between children of mothers exposed to opioid analgesics during pregnancy and children of mothers with only pre-pregnancy opioid exposure. The second comparator group consisted of children of mothers who did not report opioid exposure.

3.4.3 Outcome

Paper I: Risk assessment of medication used in pregnancy. We used internationally recognized classification systems to place each medication in risk groups according to fetal safety. The primary source was the Swedish classification system (FASS) [23]. Whenever the medication risk classification was lacking in the Swedish classification system, we used the Australian classification system [25] as a secondary source and the FDA [24] system as a tertiary classification source. The rationale for using several classification systems was to classify as many medications as possible. We chose the Swedish classification systems as the primary source because it is relevant for medications on the European market and reflects international textbook recommendations better than the FDA classification system. Based on letter categories, we grouped medication used during pregnancy into “probably safe” or “potentially risky” medications in order to make categories of more clinical interest and to facilitate the analysis. The probably safe group consisted of Swedish and Australian categories

A, B1 and B2, and the FDA categories A and B. The potentially risky group consisted of Swedish and Australian categories B3, C, D, and Australian X, and FDA category C, D and X. Medications that could not be classified by any of these sources were regarded as "not classified". More details about the classification process are described in paper I.

Paper II: Communication skills, behavior and temperamental problems. These outcome measures were parent-reported in the MoBa questionnaire at child age 5 years. Communication skills were assessed by seven questions of the communication domain of the Ages and Stages Questionnaire (ASQ) [188, 189]. This outcome was dichotomized, with T-scores ≥65 as a cutoff for clinically relevant communication problems. Selected items from the Child Behavior Checklist (CBCL) for preschool children was used to assess children's behavior [190, 191]. The CBCL has several sub-scales, which can be aggregated into externalizing or internalizing behavior. Externalizing behavior include e.g. problems with attention and aggression, while internalizing behavior include symptoms of anxiety, sadness and social withdrawal [191]. We used T-scores ≥63 as a cutoff for having clinically significant externalizing or internalizing behavior problems. Temperament was assessed by the short version of the Emotionality, Activity and Shyness Temperament Questionnaire (EAS), which measure the four temperament dimensions emotionality, activity, sociability, and shyness [192-194]. Each domain consists of three questions. Temperament was analyzed on a continuous scale, and higher T-scores indicate children who are more emotional, more active, more sociable and shyer. A brief description of the validated psychometric instruments used from the MoBa Q-5yrs is presented in Table B1, for further details please refer to paper II.

Paper III: Attention-deficit/hyperactivity disorder. The primary outcome was ADHD diagnosis in children, which was defined as a diagnosis of hyperkinetic disorder, F90 according to the International Classification of Diseases, 10th revision, recorded in the NPR and/or a filled prescription for an ADHD medication in the NorPD. As a secondary outcome, we used parent-reported ADHD symptoms in 5-year-old children. This was measured by 12 items from the Conners' Parent Rating Scale Revised Short Form (CPRS-R (S)) included in the MoBa Q-5yrs. Higher scores on the CPRS indicate more symptoms of ADHD. Scores were standardized into z-scores with a mean of zero and standard deviations of one. Z-scores of two or more were considered indicative of clinically relevant problems with attention and/or hyperactivity.

Paper IV: Scholastic skills. The outcomes were the scores from three national standardized tests on literacy, numeracy, and English language. These tests were mandatory for fifth graders (ages 10-11 years); only children with special educational

or special language training needs were exempted from a test [195]. These tests measure basic skills in literacy, numeracy and English language, and were used to assess scholastic skills. We had access to test results for the complete population of fifth graders in the period 2011-2018. Test scores were standardized as z-scores, over the total population of test takers in each subject and for each test year. A z-score of minus one indicated a test score of one standard deviation lower than the population mean. A minimally clinically important difference was not established.

3.4.4 Covariates

Table B.2 summarizes the most important covariates and confounders used in papers II-IV, in addition to their timing of measurement and source of ascertainment. More details on their definitions can be obtained from the respective papers. Risk factors for paper I is described in section 3.5.1.

3.5 Statistical analyses

All statistical analyses were performed in Stata MP (versions 14-16;StataCorpLP). This section summarizes the analyses performed.

Descriptive statistics were performed in all papers. Statistical significance was defined as a two-tailed p-value of < 0.05, when a chi-square test and the t-test or one-way analysis of variance (ANOVA) were utilized to compare proportions and means between groups, respectively.

3.5.1 Variable selection

In paper I, we sought to identify factors associated with the use of "potentially risky" medications. The following maternal factors were investigated: age, marital status, education level, working status, previous children, planned pregnancy, folic acid use, alcohol use, smoking, acute illness, and chronic disorder. To select variables to be included in the final model, we utilized the purposeful selection algorithm [196]. Candidate variables were selected based on a univariate p-value of < 0.25 and added into the multivariate model. Variables with $p > 0.05$ and $< 20\%$ impact on the beta coefficients of the retained variables were removed. The final model included significant independent variables.

In papers II-IV, we identified important variables based on subject knowledge and with the aid of DAGs [197, 198]. DAGs graphically encode relationships between variables and make it possible to distinguish between variables that need to be controlled for and which variables should not be controlled for. Moreover, employing DAGs require to set

assumptions about causal relationship and the direction of the association between variables [197, 199]. The DAGs utilized in papers II-IV are presented in the supplementary material of the respective papers.

3.5.2 Propensity score methods for control of confounding

In papers II-IV, we used propensity scores with weighting to control for measured confounders. The propensity score is the probability of exposure given the observed baseline characteristics [166]. Among persons with a given propensity score, the distribution of the covariates is on average the same among the exposed and unexposed [166]. This section will briefly and in general terms, describe how the propensity scores were estimated and applied in the different papers. Please refer to the respective paper for more details. Propensity scores were estimated by fitting a logistic regression model for every exposure-reference combination, estimating the probability of exposure conditional on measured baseline covariates. The propensity score models included confounders and risk factors for the outcome as recommended [200]. Based on the estimated propensity score, we derived stabilized inverse probability of treatment weights (IPTW) (papers II-IV), and standardized mortality/morbidity ratio weights (SMR) (paper IV). For a description of how this is calculated, please refer to the paper by Stürmer et al. [164]. Balance of covariates among exposed and unexposed was assessed by standardized differences and a standardized difference of <0.10-0.15 were considered acceptable [201, 202]. Visual inspection of the weights was performed in order to detect extreme weights.

3.5.3 Missing data and multiple imputation

In Paper I, participants with missing data on maternal factors were excluded from the analysis. Missing values were less than 5% of the total. In paper II, we performed a complete case analysis. Participants with missing data on important covariates, those lost to follow-up or with no outcome data at five years were excluded from the analyses. Eleven percent had missing information on at least one of the important confounders. In papers III and IV, we used multiple imputation to replace missing values on confounders. We assumed the variables to be missing at random and we used multiple imputations by chained equations in order to allow for the specification of the imputation model [176]. The imputation model included information on exposures, outcomes and auxiliary variables, as recommended [175]. In paper III, the primary outcome was modelled as time-to-event. To account for this, the imputation model included the cumulative Nelson Aalen hazard function for the outcome [203]. More information about the imputation process and variables included in the imputation model can be found in the respective papers.

3.5.4 Regression analyses

Paper I: Generalized Estimating Equations (GEE) with a binomial distribution were used to examine factors associated with the use of "potentially risky" medications during pregnancy (dichotomous variable: potentially risky medication user versus probably safe medication user). GEE were used in order to account for any clustering on region of residence [204]. Data are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Paper II: Communication skills and child behavior were analyzed as categorical outcomes and we used generalized linear models (with a negative binomial distribution) to calculate crude relative risks (RR). For temperamental traits, which was analyzed on a continuous scale, we used linear models to obtain crude estimates. Robust standard errors were used to calculate 95% CI. In order to account for loss to follow-up at 5 years, we utilized inverse probability of censoring weights, which up-weighted the participants who remained to represent similar women who dropped out from the baseline sample. These weights were multiplied with the obtained IPTW, and the combined weight was added to the outcome models to obtain weighted estimates.

Paper III: Cox regression with robust standard errors was used to estimate crude and weighted hazard ratios (wHR) of ADHD diagnosis with 95% CI. We used child age in years as time scale and a quadratic term for the year of birth in the outcome model. Children were followed from birth until the date of an ADHD diagnosis, date of an ADHD medication prescription or until December 31 2016, whichever came first. To estimate standardized mean differences (β) in ADHD symptoms, generalized linear models with robust standard errors were used.

To account for missing data in these analyses, we multiple imputed 10 datasets. Propensity scores and subsequent weights were estimated in each imputed dataset and then regression analyses were run in each dataset. The results of all imputed sets were combined using Rubin's rule [205] to obtain an overall estimate [206].

Paper IV: Generalized linear models were used to estimate mean differences in z-scores of national tests results. Results are presented as standardized mean differences (β) and 95% CI.

To account for missing data in these analyses, we used 30 multiple imputed datasets for each outcome: literacy, numeracy, and English tests. Propensity scores and the respective weights were estimated in each imputed dataset before regression analyses were run in each set. The results of all imputed sets were combined using Rubin's rule [205] to obtain an overall estimate [206].

3.5.5 Sensitivity analyses

In paper I, we described the safety profile of the 10 most frequently used analgesics. In paper II, we performed several sensitivity analyses to explore the role of unmeasured confounding, e.g. a negative control analysis, bounding factor analysis and we explored the treatment effect across different strata of the propensity score for the main findings. In paper III, we performed sensitivity analyses to test the robustness of our findings (e.g. complete case analysis and alternative model specifications that took into account additional paternal and child factors). We also performed analysis stratified by child sex and we calculated the e-value to examine the role of unmeasured confounding. In addition, we crosschecked maternal self-reported opioid use with NorPD data and looked at the average defined daily dose (DDD) dispensed to describe the amount of opioids in paper III. In paper IV, we conducted a complete case analysis and we performed analysis stratified by child sex. For more details, please refer to the respective papers.

4 Main findings

The main findings are presented separately for each paper. Figure 4.1 shows an overview of the main findings from the four papers in relation to the overall aims of this thesis.

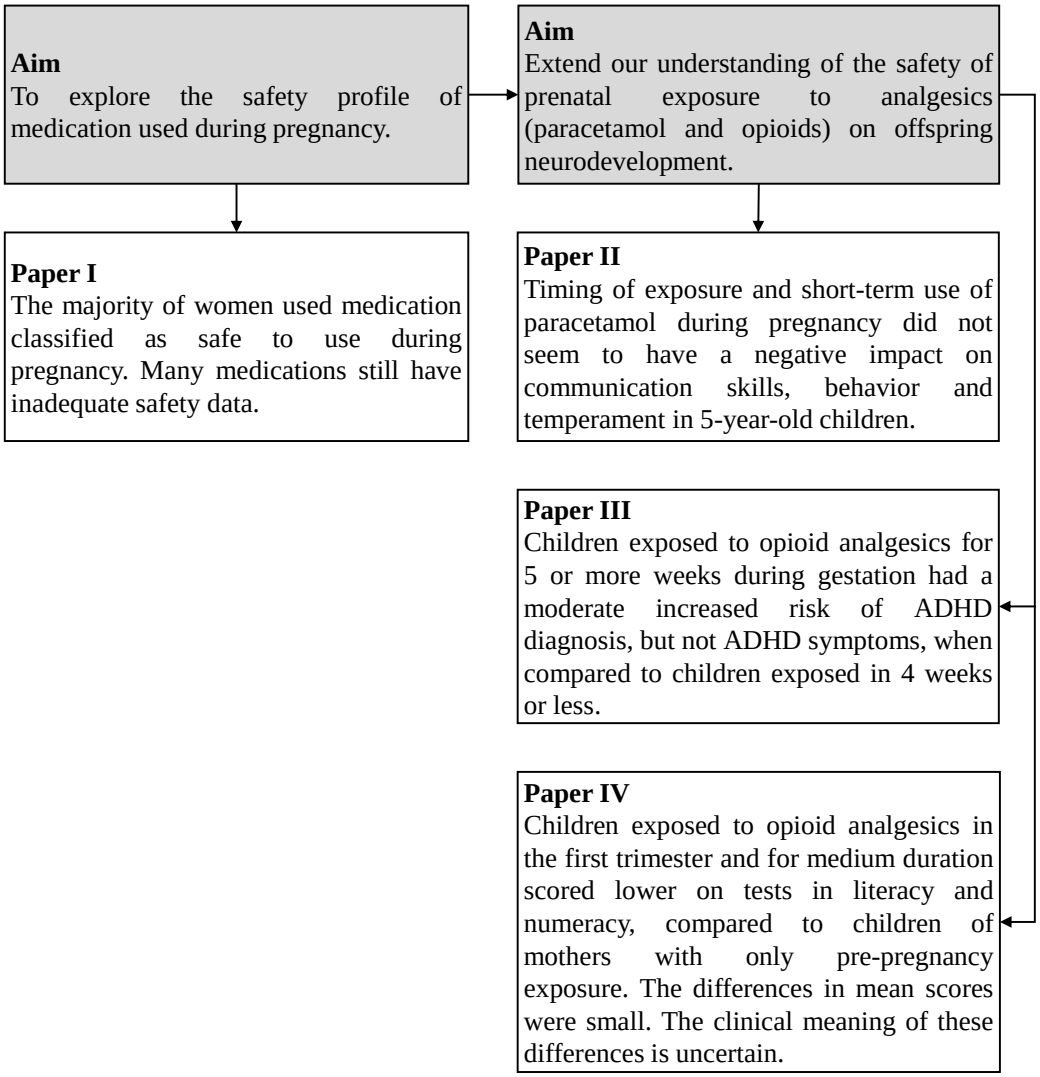


Figure 4.1 Main findings of this thesis in relation to the overall aims of this thesis.

4.1 Paper I: Safety profile of medication used during pregnancy

In this study, 6657 women from 15 European countries were included. Of these, 3455 (51.2%) women were pregnant at the time they completed the questionnaire and the remaining were mothers with a child less than one year of age. The number of participants in each of the European regions were as follows:

- **Western Europe:** Austria (n=62), France (n=321), Italy (n=633), Switzerland (n=503), the Netherlands (n=77), and the United Kingdom (n=947).
- **Northern Europe:** Finland (n=526), Iceland (n=66), Norway (n=994) and Sweden (n=769).
- **Eastern Europe:** Croatia (n=177), Poland (n=513), Russia (n=815), Serbia (n=150) and Slovenia (n=104).

In total, 587 different medications were reported. Of these, 38% were classified as probably safe medications to use during pregnancy, 39% were classified as potentially risky medications, and 23% of the medications could not be assigned any risk category in pregnancy. For more details, see Figure 2 in paper I.

The majority of women (n=4569, 69 %) used medications classified as probably safe. Paracetamol, ordinary salt combinations, and alginic acid were the most frequently used medications in this group. Twenty-eight percent of the women (n=1881) used medications classified as potentially risky, and the most frequently used medications in this group included ibuprofen, metoclopramide, and codeine (combined products excluding neuroleptics). Under 3% (n=180) of women used medication with no classification available. The ones most frequently used in this group were drotaverine, hydrotalcite, and combinatory nasal preparations (for more details, see Table 2 in paper I).

The majority of women across all countries used medications that are probably safe to use during pregnancy (Figure 4.2). A higher proportion of women from Northern Europe used potentially risky medications during pregnancy compared with women from the other regions. The highest proportion of women using unclassified medications were from Eastern Europe.

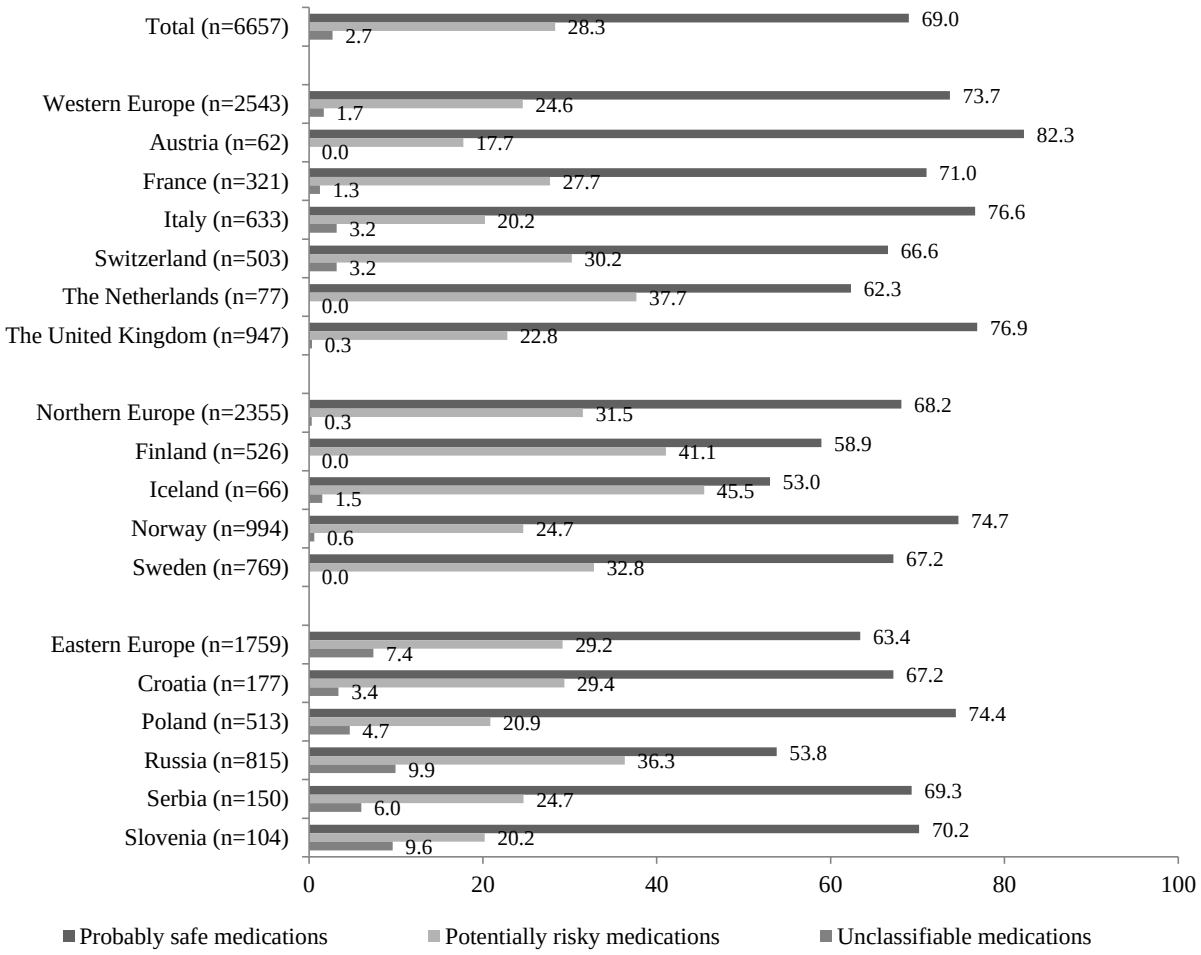


Figure 4.2 Proportion of women using medications according to safety profile, by region and country of residence.

Figure obtained from Trønnes et al. 2017 [36].

We found that being a student, housewife or working as healthcare personnel, having previous children, not using folic acid, consuming alcohol and smoking were associated with the use of potentially risky medications, with magnitude of associations ranging between 10% and 30% increased odds (Table 4.1). Having a chronic disorder was the factor with the strongest association with the use of potentially risky medications during pregnancy (aOR: 3.99, 95% CI: 6.54, 4.49). This finding was consistent in country-specific analyses.

Table 4.1 Factors associated with use of potentially risky medications during pregnancy.

Maternal characteristics	OR (95% CI)	Adjusted OR (95% CI)
Age (as continuous variable)	1.01 (0.99-1.02)	-
Marital status		
Married or cohabiting	Reference	-
Single/divorced/other	1.29 (1.01-1.63)	-
Education level		
Less than high school	1.40 (1.08-1.81)	1.20 (0.91-1.58)
High school	Reference	Reference
More than high school	1.07 (0.94-1.21)	1.10 (0.96-1.27)
Other	1.19 (0.99-1.43)	1.23 (1.01-1.50)
Working status		
Student	1.25 (1.03-1.51)	1.33 (1.09-1.63)
Housewife	1.40 (1.15-1.70)	1.29 (1.04-1.59)
HCP	1.28 (1.09-1.49)	1.31 (1.11-1.54)
Employed in other sector	Reference	Reference
Job seeker	0.97 (0.74-1.28)	0.92 (0.68-1.23)
None	1.08 (0.84-1.39)	0.93 (0.71-1.21)
Previous children		
Yes	1.13 (1.02-1.26)	1.14 (1.02-1.28)
No	Reference	Reference
Planned pregnancy		
Yes, not completely unexpected	Reference	-
No, it was not planned	1.21 (1.01-1.46)	-
Folic acid use before and/or during pregnancy		
Yes	Reference	Reference
No	1.26 (1.04-1.53)	1.26 (1.02-1.55)
Alcohol use after awareness of pregnancy		
Yes	1.28 (1.11-1.47)	1.29 (1.11-1.50)
No	Reference	Reference
Smoking during pregnancy		
Yes	1.30 (1.09-1.56)	1.30 (1.07-1.59)
No	Reference	Reference
Acute illness		
Yes	0.96 (0.46-1.99)	-
No	Reference	-
Chronic disorder		
Yes	3.93 (3.49-4.42)	3.99 (3.54-4.49)
No	Reference	Reference

For all binary variables, the reference category was No, except for Folic acid use and Planned pregnancy. For Folic acid use and Alcohol consumption, the response `cannot remember` was treated as a missing value. Table obtained from Trønnes et al. 2017 [36].

In total, 5190 women (78%) reported use of analgesics during pregnancy. In Table 4.2, the 10 most frequently reported analgesics are listed, along with their respective pregnancy safety classification.

Table 4.2 Safety classification of analgesics.

Top 10 analgesics	n (%)	Probably safe medications	Potentially risky medications	Unclassified medications
Paracetamol	4459 (67.0)	●		
Ibuprofen	309 (4.6)		●	
Acetylsalicylic acid	96 (1.4)		●	
Paracetamol, comb excl. psycholeptics	75 (1.1)	●		
Diclofenac	35 (0.5)		●	
Metamizole sodium	29 (0.4)			●
Ketoprofen	18 (0.3)		●	
Tramadol	16 (0.2)		●	
Naproxen	10 (0.2)		●	
Mefenamic acid	10 (0.2)		●	

Women may have used more than one medication. Study sample, n=6657.

4.2 Paper II: Prenatal exposure to paracetamol and neurodevelopmental outcomes

In this study, we included 32 934 children. Of these, 15 126 (45.9 %) children were exposed to paracetamol at least once during gestation. Among the exposed children, the majority were exposed in one trimester (55.4%), while 32.8% and 11.8% were exposed in two and three trimesters, respectively. Women who used paracetamol during pregnancy were less likely to be first-time mothers, used co-medications more frequently, had more health problems, smoked more, and reported a low to moderate intake of alcohol more often than women reporting no use of paracetamol during pregnancy. In total, 7.5% of children in the study sample had communication problems, 9.8% of children had externalizing behavioral problems, and 10.3% of children had internalizing behavioral problems.

Timing of prenatal exposure to paracetamol was not associated with increased risk of communication, behavioral or temperamental problems in 5-year-old children. However, children exposed in $2^{nd}/3^{rd}$ trimester scored lower on shyness (weighted β (w β): −0.32, 95% CI: −0.66, 0.02) compared to unexposed children.

In analysis of duration, we found an increased risk of internalizing (weighted Relative Risk (wRR): 1.36, 95% CI: 1.02, 1.80) and externalizing behavior problems (wRR: 1.22, 95% CI: 0.93, 1.60) in children whose mothers used paracetamol in three trimesters compared to unexposed children. Although the latter confidence interval included the null. Further, children of mothers who used paracetamol in two trimesters, scored lower on shyness (wβ: −0.62, 95% CI: −1.05, −0.19) compared to unexposed children. We did not observe any associations between prenatal paracetamol exposure and communication problems or other temperamental problems in 5-year-old children.

In the negative control analysis, paracetamol use only prior to pregnancy was associated with communication problems (wRR: 1.19, 95% CI: 1.02, 1.38) and lower activity levels in children (wβ −0.80, 95% CI: −1.23, −0.36). We observed a non-uniform treatment effect across different strata of the PS for the effect of paracetamol exposure in multiple trimesters on internalizing behavior and on shyness (for more details, please refer to the supplementary material of paper II). A confounder with strength equal to RR of 2.06, would be needed in order to explain away the observed association between paracetamol exposure and internalizing behavior problems.

4.3 Paper III: Prenatal exposure to opioid analgesics and ADHD

A total of 73 480 children were included for the analysis on ADHD diagnosis and we had data on 31 270 children for the analysis on ADHD symptoms. Use of opioid analgesics was reported in 2.1% to 2.3% of pregnancies with codeine combined with paracetamol being the most frequently used opioid (reported in 90.0 % of exposed pregnancies). In total, 3.0 % of children had an ADHD diagnosis and the mean (SD) follow-up time was 10.8 (2.2) years. Regarding parent-reported ADHD symptoms at age 5 years, 4.8% had a z-score of two or more standard deviations from the mean. Most women had a college or university education, but mothers of children with exposure were more likely to report smoking, alcohol, and use of co-medications during pregnancy.

Timing of prenatal exposure to opioid analgesics was not associated with an increased risk of ADHD diagnosis when compared with no exposure, nor when compared with pre-pregnancy exposure only. In crude analyses, we observed an association with exposure in early and middle and/or late pregnancy and higher incidence of ADHD diagnosis (early exposure: Hazard Ratio (HR): 1.76, 95% CI: 1.30, 2.36: middle and/or late exposure: HR: 1.76, 95% CI: 1.38, 2.25) when compared with no exposure. However, upon weighting the point estimates were attenuated and the association was

no longer seen (early exposure: weighted HR (wHR): 1.34, 95% CI: 0.90, 2.02; middle and/or late exposure: wHR: 1.32, 95% CI: 0.92, 1.89), pointing to the importance of confounder adjustment. The point estimates were lower in analyses with pre-pregnancy exposure as reference and the estimates included the null (early exposure: wHR: 1.13, 95% CI: 0.71, 1.79: middle and/or late exposure: wHR: 1.08, 95% CI: 0.70, 1.68). In the analysis of length of exposure, we observed an increased risk of ADHD diagnosis after prenatal exposure for 5 or more weeks when compared to exposure for 4 or fewer weeks (wHR: 1.60, 95% CI: 1.04, 2.47).

In the secondary analysis on ADHD symptoms at age 5 years we found no associations between timing or length of prenatal exposure to opioid analgesics and higher symptom scores.

Point estimates under alternative model specifications and from the complete case analysis were generally consistent with main findings. In analyses stratified by sex, we found no difference between boys and girls with regard to ADHD risk or higher ADHD symptoms. The calculated e-value of 2.58 indicated that we would need an unmeasured confounder with a strong association with the exposure and outcome to explain away the association in the duration analysis. In a subsample of participants with data available in both MoBa and NorPD (50 925 mother-child pairs), the mean defined daily dose (DDD) dispensed among women using opioids for 4 or fewer weeks and 5 or more weeks were 8.6 DDD and 37.2 DDD, respectively.

4.4 Paper IV: Prenatal exposure to opioid analgesics and scholastic skills

In this study, we included 64 256 pregnancy-child pairs. Use of opioid analgesics was reported in 2.3% of pregnancies (n=1483), the most reported substance being codeine combined with paracetamol. Most women reported short-term use (n=937/1483 = 63.2%), that is use in one 4-week interval in pregnancy. Mothers of exposed children were slightly older, more likely to have previous children and to report use of alcohol and co-medications, compared to mothers who used analgesic opioids before pregnancy only.

The majority of children (96.2%) participated in all three tests: literacy, numeracy and English. Children ever exposed to opioid analgesics in pregnancy scored similarly to children of mothers with pre-pregnancy exposure only. Exposure to opioid analgesics in first trimester was associated with lower scores on tests in literacy (wβ: −0.13, 95% CI: −0.25, −0.01) and numeracy (wβ: −0.14, 95% CI: −0.25, −0.04) compared to

children of mothers with pre-pregnancy exposure only. Prenatal exposure to opioid analgesics in second or third trimester was not associated with lower scores in any of the subjects, although we observed a trend towards lower scores. In the analysis on duration, only children exposed in the middle duration category (2-3 4-week intervals) scored significantly lower on tests in literacy (wβ: −0.19, 95% CI: −0.35, −0.04) and numeracy (wβ: −0.19, 95% CI: −0.34, −0.05) compared to children of mothers with pre-pregnancy exposure. Prenatal exposure in any other duration category was not associated with significantly lower scores.

In analyses stratified by sex, we found no difference between boys and girls, as the point estimates were of similar magnitude and confidence intervals were overlapping.

When unexposed children acted as comparator, we found no association between prenatal exposure to opioid analgesics and lower scores on tests in literacy, numeracy or English in any trimester or duration category.

5 Discussion

5.1 Summary of main findings

Paper I: The majority of women used medication classified as safe to use during pregnancy. Twenty-eight percent of the women used medications classified as risky. We observed differences with respect to the use of medications in different risk groups both at regional and country level. Both socio-demographic and medical factors were associated with the use of risky medications during pregnancy and having a chronic disorder was the strongest driver for such use. One out of five medications used could not be assigned any risk category in pregnancy.

Paper II: Prenatal exposure to paracetamol was reported in 45.9% of the sample. Timing of exposure and short-term use of paracetamol during pregnancy did not seem to have a negative impact on communication skills, behavior and temperament in 5-year-old children. Compared to those unexposed, children exposed to paracetamol in two trimesters scored lower on shyness. Children exposed to paracetamol in three trimesters had a moderate increased risk of internalizing and externalizing behavior problems compared with unexposed children. Children exposed to paracetamol in 2nd and / or 3rd trimester scored lower on shyness compared with unexposed children. Sensitivity analyses indicated that unmeasured confounders play an important role on these associations.

Paper III: Opioid analgesic use during pregnancy was reported in 2.3% and 2.1% of pregnancies in the ADHD diagnosis sample and the ADHD symptom sample, respectively. Approximately 3.0% of children had an ADHD diagnosis. We observed no increased risk of ADHD diagnosis, or higher symptoms at age 5 years, according to timing of exposure in pregnancy, when compared to both unexposed children and children with only pre-pregnancy exposure. Children exposed for 5 or more weeks had a moderate increased risk of ADHD diagnosis when compared to children exposed in 4 weeks or less. There was no such association for the risk of ADHD symptoms.

Paper IV: Opioid analgesic use during pregnancy was reported in 2.3% of the sample. Children with any exposure to opioid analgesics during pregnancy scored similar on national standardized tests in fifth grade, compared to those children of mothers with only pre-pregnancy exposure. Exposure to opioid analgesics in the first trimester or during two to three 4-week intervals during pregnancy was associated with lower scores in literacy and numeracy, compared to only pre-pregnancy exposure. The differences in mean test scores were small and the clinical meaning of these differences is uncertain.

5.2 Interpretation and comparison of findings

5.2.1 Safety profile of medication used during pregnancy

No previous study has examined the safety profile of medication used during pregnancy and maternal factors associated with risky medication use during pregnancy across several European countries. This study adds to the literature by having a uniform collection of data on medication utilization across countries.

One important finding is that the majority of women, at an aggregated level, used medication classified as safe to use during pregnancy. This is reassuring. However, a considerable proportion still used medication classified as potentially risky. Avoiding all potentially risky medications during pregnancy may be unrealistic as some conditions require treatment (e.g. epilepsy, diabetes, and infections) [207]. Taking a medication during pregnancy involves weighing potential risks versus benefits. Avoiding necessary treatment may endanger maternal-fetal health, while unnecessary medication use may potentially harm the fetus [6]. Many of the potentially risky medications are used during pregnancy when safer alternatives are not available or switching of medications is not recommended [207]. However, this study is limited to describe medication utilization patterns and cannot evaluate the appropriateness of medication use or treatment of the individual women.

Other studies have also reported the use of potentially risky medication during pregnancy [2]. However, direct comparison between studies may be challenging due to different methodology. In previous studies based on the FDA classification, estimates of prescription medications in the D/X category range from 3% in Italy [44], 5.0% in Ireland [42], 5.8% in the USA [45] to 12.5% in China [39]. Previous studies that were mainly based on the Swedish or the Australian classification system estimated that 2.2% in France [34], 12% in the Netherlands [47], and 20% in Finland [48] were prescribed medications with potential for fetal harm during pregnancy. Our study classified medications primarily based on the Swedish classification system and our findings are to some extent in line with previous findings. Possible explanations for the observed differences could be related to different classification systems used, different methodology used to assess medication use, and that our study also included the use of over-the-counter medications. In addition, some of these studies were published more than 15 years ago and utilization patterns may have changed since then. Variation in prevalence estimates may also be due to different health needs of the pregnant population or differences in marketed medications in the individual countries.

Knowledge about factors associated with the use of potentially risky medications during pregnancy may help identify women who could benefit from pre-pregnancy counseling to optimize medication use during pregnancy. Few studies have investigated maternal characteristics associated with use of potentially risky medications during pregnancy. One study found that being eligible for a disability allowance, chronic diseases, use of five or more medications, alcoholism and illicit drug use were the strongest maternal characteristics associated with increased risk of potentially harmful medication prescribing during pregnancy [34]. Another study found that having chronic health conditions, being above 20 years of age, having more than three previous children or being on social assistance plan increased the risk of being exposed to such potentially harmful medications [208]. A third study also reported that women having a chronic health condition and with previous children were more likely to use potentially harmful medications during pregnancy [46]. In Paper I, several factors were associated with the use of potentially risky medications during pregnancy. These were being a student, homemaker or working as healthcare personnel, having previous children, not using folic acid, consuming alcohol, smoking and having a chronic disorder. These results shows both similarities and differences to the previous literature. Overall, having a chronic condition was consistently reported to be associated with use of potentially risky medications. However, such use may still be appropriate considering the woman's underlying illness, but individual risk-benefit evaluations should be conducted. Furthermore, concerning the factors identified in our study, women with health related occupations may be more knowledgeable about the risks of untreated illnesses during pregnancy [209]. Women with previous children are likely to be at an older age and thus more likely to have pre-existing conditions requiring medical attention [31]. Women who smoke or consume alcohol during pregnancy may have a less restrictive attitude toward medication use [210].

In our study, we found that one out of five medications could not be assigned any risk category in pregnancy. Interestingly, the highest proportion of women using unclassified medications were from Eastern Europe. This could be because many of the medications used in Eastern Europe may not be on the market in Northern Europe, U.S., or Australia and may lack a classification in the three reference systems used in the current study. Other studies have also been unable to classify medications, although the proportion may have been somewhat smaller than in our study [34, 44, 47]. Many medications still lack or have inadequate safety data for use among pregnant women and their children. More studies on medication safety in pregnancy are needed to fill these knowledge gaps.

Among the most frequently used analgesics in this study, we find paracetamol, NSAIDs and tramadol (Table 4.2). Paracetamol belongs to FASS category A and was classified as safe to use during pregnancy. Whereas NSAIDs and tramadol belong to FASS category C, and were classified as potentially risky [23]. The reason for classifying these medications as potentially risky is related to risks described in the Introduction. The letter categories of the risk classification systems primarily refer to teratologic risk as the major adverse outcome of pregnancy [29]. However, the reproductive safety of a medication cannot be assured without considering both immediate- and long-term safety. It should be noted that risk assessment is challenging, as there are many things to consider, e.g. the maternal underlying illness. The risk classification systems have received much criticism [4, 211]. Partly because the letter categories does not address the issue that the risk is non-uniform throughout the different stages of pregnancy and partly because they convey the incorrect impression that there is a gradation of reproductive risk from medication exposure across categories [29]. We chose the Swedish classification systems as the primary classification source because it is relevant for medications on the European market and reflects international textbook recommendations better than the FDA classification system [20, 80]. In 2015, the FDA abandoned their pregnancy risk category letter system [26]. Today, data from observational studies are increasingly incorporated into labelling and provide real-world safety information about dosing and fetal risks [7].

5.2.2 Prenatal exposure to paracetamol and neurodevelopmental outcomes in children

Paper II builds on previous research within the MoBa. The same neurodevelopmental outcomes were measured in children at ages 1.5 [96] and 3 years [72]. As problems detected in early childhood may change or evolve [212], it was considered important to reassess neurodevelopment in the same cohort at a later stage. In addition, some problems are detected more easily when the child is older [155]. In a propensity-score matched analysis, Vlenterie et al. [96] found that long-term exposure to paracetamol during pregnancy (more than 28 days) was associated with communication problems and delayed motor milestone attainment in children at 1.5 years. In a sibling-control analysis among 3-year-old children, children exposed to paracetamol for more than 28 days during gestation had poorer gross motor development, communication skills, more externalizing and internalizing behavior problems, and higher activity levels [72]. After 5 years of follow-up, only internalizing behavior problems remained significant, although the risk of externalizing behavior was elevated. We could not replicate the association with communication or activity problems. Further, in 5-year-old children we observed that children exposed in multiple trimesters scored lower on shyness; however, the clinical meaning of this is uncertain. A possible explanation for the

different findings could be that problems detected in early childhood have resolved by 5 years of age. However, direct comparison may be challenging because of different analysis methods and exposure classification. About 56% of the women reporting use of paracetamol for 28 days or more were classified as exposed in three trimesters in our study.

Interestingly, a study using data from the 2004 Pelotas birth cohort in Brazil have also assessed child behavior using the Child Behavior Checklist [213]. In contrast to findings from the MoBa cohort, there was no association between paracetamol exposure during pregnancy and increased internalizing or externalizing problems in 4-year old children from the Pelotas cohort [213]. This study has certain limitations that should be noted, e.g. retrospective exposure ascertainment, broad question used to assess exposure status (ever versus never) and residual confounding by indication.

Other studies have mainly focused on behavioral outcomes, in particular ADHD [76]. Some studies have used ADHD diagnosis to define the outcome [87, 95, 167, 214-216], whereas others have used parent and/or teacher report [72, 88, 92, 94, 96-98, 213, 217-220]. Studies using diagnostic outcomes have identified higher incidence of ADHD after prenatal exposure to paracetamol, whereas most of the studies using parent-report identified more behavioral problems among exposed children [72, 94, 97, 98, 217, 218]. Based on the current literature, positive associations are primarily seen in relation to long-term exposure or high-dose paracetamol use during pregnancy [108]. Measuring the duration of exposure is challenging as self-reported data is dependent on the accuracy of recall and may be limited by misclassification bias. Most studies based on the MoBa cohort have used “number of days” to define long-term exposure [72, 95, 96, 167]. To the best of our knowledge, this exposure classification was based on findings from a Danish study, finding positive association between prenatal paracetamol exposure for more than four weeks and increased risk of cryptorchidism [79]. In paper II, we used number of trimesters with reported exposure as a proxy of duration. Future studies should try to incorporate information on frequency and dosage.

Bias from unmeasured confounding have been a concern within this literature. Several approaches have been used to evaluate the presence of unmeasured confounding, such as negative control analysis [95, 97, 215] and sibling design [72, 167]. However, the findings are conflicting. In paper II, we found positive associations between our negative control group and some child outcomes, though different outcomes than those identified in the main analysis. This may suggest that bias from unmeasured factors drive estimates away from the null. Similar to our study, Ystrom et al. [95] identified an association between the negative control group and the outcome. When investigating hereditary conditions, such as ADHD, genetic factors should be taken into consideration

[221]. In a systematic review, Masarwa et al. [222] illustrated with probabilistic bias analysis how adjustment for parental ADHD alone or in combination with maternal migraine could explain away all associations between prenatal paracetamol exposure and ADHD. Furthermore, the fact that multiple biases (selection, information and confounding) may act simultaneously should be kept in mind. How this might drive associations, was nicely elaborated in the commentary by Wood et al. 2020 [100]. In paper II, we additionally explored the treatment effect within different strata of the propensity score to assess unmeasured confounding. Our findings from these analyses indicated a non-uniform treatment effect across different strata of the propensity score. These findings support presence of unmeasured confounding [223]. Trimming of the propensity score attenuated the results.

Establishing the neurodevelopmental safety of paracetamol use during pregnancy is challenging. There is a range of domains within the realm of neurodevelopment. Some have questioned the validity of the survey-based instruments used to measure neurodevelopment [85]. Others have questioned whether psychiatric diagnosis are sensitive enough to capture subtle changes [156, 157]. The question of whether associations are causal or due to bias still remain unresolved [100, 222, 224]. Differing opinions exist. On one hand there is a part of the scientific community that call for precautionary action [108], whereas others believe the evidence is not strong enough [75, 225]. Although one can agree that no one should use medications that are not needed and long-term use should be evaluated on an individual basis with a physician. The European Medicines Agency reviewed the available literature in 2019, and concluded that paracetamol is still safe to use during pregnancy, but emphasized the inconclusive nature of the evidence in the literature [107]. The summary of product characteristics of all paracetamol products in Europe were updated with the following wording: *"Epidemiological studies on neurodevelopment in children exposed to paracetamol in-utero show inconclusive results".*

Our findings are in line with current guidelines that recommend paracetamol be used at the lowest effective dose for the shortest possible time. Pregnant women should be empowered to make appropriate decisions about their use of paracetamol during pregnancy to avoid both overuse and underuse, and avoid unfounded concerns about the risks of paracetamol to the unborn child.

Future studies should provide analyses by dose or duration and preferably having more detailed information on these measures. Studies should employ multiple-informant methods and careful follow-up of participants. In addition, it is necessary to carefully consider how bias from various sources (such as exposure misclassification, selection and residual confounding) could work together driving effect estimates in either

direction. Genetic factors should be taken into consideration when investigating hereditary conditions, such as ADHD to strengthen the inference [226].

5.2.3 Prenatal exposure to opioid analgesics and neurodevelopmental outcomes in children

The literature examining neurodevelopmental outcomes in children after prenatal exposure to opioid analgesics is limited [76]. Papers III and IV have investigated the risk of ADHD and scholastic performance, respectively. These outcomes are important to study, as they may have a major impact on a child's daily functioning. Moreover, scholastic skills are infrequently assessed in perinatal pharmacoepidemiological studies [227, 228]. In paper III, we found a slightly increased risk of ADHD diagnosis after prenatal exposure to opioid analgesics, which may be driven by longer duration of use. In paper IV, children exposed to opioid analgesics in the first trimester and for medium duration scored lower on tests in literacy and numeracy, compared to children of mothers with only pre-pregnancy exposure. The differences in mean test scores were small and thus, they should be interpreted with caution. Moreover, on all tests, the mean test scores among the exposed children were above the population mean, which indicated that their performance was not worse than that of the general population of fifth graders. We believe these findings are reassuring for pregnant women that need to use opioid analgesics for pain management during pregnancy. However, treatment should be discussed on an individual basis and long-term use or high doses should be avoided, in accordance with the current guidelines.

In papers III and IV, approximately 90% of women who reported use of opioid analgesics, reported use of codeine combined with paracetamol. Disentangling the sole effect of opioids may thus be challenging. Positive associations have been reported between paracetamol use during pregnancy and ADHD [87, 95], although the causal relationship is still unresolved (see section 5.2.2). Furthermore, women who use codeine combined with paracetamol may have used paracetamol alone previously. In addition, the combined product may be used under circumstances that are more heterogeneous than stronger opioids, and we cannot rule out residual confounding.

Previous studies have examined domains including; language and communication [122, 124], risk of ADHD [123], autism spectrum disorder [73] and neurodevelopmental disorders in early childhood (several disorders grouped together) [67].

The study by Azuine et al. [123], found that prenatal opioid exposure was associated with a higher risk of ADHD diagnosis in school-aged children (OR: 2.55, 95% CI: 1.42, 4.57) when compared to children with no exposure. A potential drawback with this study is that opioid exposure included both prescription and illicit opioids, and children

with a clinical diagnosis of neonatal abstinence syndrome. This makes it difficult to estimate the direct effect of opioids [229] and also to compare with findings from paper III. In addition, Azuine et al. does not take into account timing or duration of exposure, and that ADHD is highly heritable. In paper III, we accounted for proxies of familial risk of ADHD by including whether parents filled a prescription for an ADHD medication or not, which is a strength of our study. We also explored the effect of exposure timing and exposure duration. Reassuringly, timing was not associated with increased risk of ADHD. Regarding duration of exposure, children exposed for 5 or more weeks had a slightly increased risk of ADHD diagnosis compared to children exposed in 4 weeks or less (HR: 1.60, 95% CI: 1.04, 2.47). For the analysis on duration, we were not able to make more granular exposure groups and to compare with unexposed children or children with pre-pregnancy exposure only. This because of large imbalances in covariates between groups. Although sensitivity analysis confirmed that those exposed for a longer period had received more than those exposed for shorter duration, a possible dose-response relationship needs to be further investigated.

Wen et al. [67] reported that prenatal exposures for >14 days or exposures to high cumulative opioid doses increased the risk of neurodevelopmental disorders (HR range: 1.22-1.70), compared to no exposure. The outcomes investigated included a range of domains adopted from the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for neurodevelopmental disorders (including intellectual disability and ADHD). The average follow-up time was 2.5 years. This follow-up time might be a little short, however, they also performed sensitivity analysis in children with more than 5 years of follow up. In that analysis the point estimate was elevated but the confidence interval included the null (adjusted HR: 1.42, 95% CI: 0.87, 2.33).

To date there are, to the best of our knowledge, four studies based on MoBa data examining neurodevelopmental outcomes following prenatal exposure to opioid analgesics (including papers III and IV).This provides some foundation to look at how these children develop over time, although there are some distinct differences in methodology and outcome measure that limits direct comparison. Skovlund et al. [122, 124], found no increased risk of reduced language and communication skills in 3 and 5 year old children. Because language development plays a fundamental role in cognition and learning, early language deficits may impair long-term cognitive development and academic achievement [230, 231]. The findings from paper IV is therefore in accordance with previous findings from the same cohort. If there was a strong effect of prenatal exposure to opioid analgesics on cognitive development, we would have expected signals in younger children. However, it is too early to draw any conclusions, and more studies are needed. Future studies should investigate other domains of

neurodevelopment. In addition measures of dose, duration and type of opioid should be included. International collaborative studies among countries could help to increase sample sizes. Findings need to be replicated across different study sites. The choice of comparator group should be carefully considered, as opioid analgesics are used for moderate to severe pain, and unexposed population comparators may not be appropriate.

5.3 Methodological considerations

This section presents methodological considerations that should be kept in mind when interpreting the thesis findings.

5.3.1 Selection bias and representativeness

The Multinational Medication Use in Pregnancy study recruited women via placement of banners on websites frequently visited by pregnant women. By using this approach, a conventional response rate cannot be calculated. However, 98.6% of the women confirmed their willingness to participate after reading the study description. We cannot rule out the possibility for self-selection bias because respondents were women who had Internet access, happened to visit the website(s), and decided to participate in the study. Lupattelli et al. [3], found the study sample to be representative of the general birthing population on an individual country level with respect to age, parity, and smoking habits. However, the sample had a higher education level than the general birthing population in each country.

In the MoBa study, 41% of the invited women consented to participate [134]. The low response rate and the possibility of self-selection may have introduced selection bias. Nilsen et al. [132] have compared the study participants to the general birthing population in Norway and found that MoBa participants were less likely to be young mothers, more likely to be married or cohabiting, and had a healthier lifestyle during pregnancy. Therefore, we cannot rule out that selection bias have affected our results in papers II-IV.

5.3.1.1 Loss to follow-up

This section applies to papers II and III where we were dependent on the parents completing the follow-up questionnaire in MoBa when their child was 5 years old. It is common that participants are lost to follow-up in cohort studies and approximately 50% of the eligible parents completed the questionnaire at 5 years [232]. A recent study showed that the loss to follow-up appeared to bias estimates of association for long-term outcomes [233]. This study also suggested that inverse probability of censoring

weights was a robust method to handle such bias [233]. Therefore, we used inverse probability of censoring weights in paper II to reduce bias from loss to follow-up. This approach was not utilized in paper III and we cannot rule out that selection bias due to loss to follow-up have affected our results on the ADHD symptom measure.

5.3.1.2 Live-birth bias

Papers II-IV studied outcomes that are only observable in live-born children. Therefore, we restricted our analyses to live births. This may have introduced bias [234, 235]. We believe the outcome, or a susceptibility for the outcome, is determined during fetal life. The population at risk would therefore be "all conceptions" and pregnancy loss would be a competing risk. In this scenario, bias may occur if the exposure is a cause of both the outcome and pregnancy loss, with the latter two also sharing an unmeasured common cause. Paracetamol use is not associated with non-live births [77], but the evidence regarding opioid analgesic use is less clear [20]. If opioid analgesics are associated with non-live birth, we cannot rule out that conditioning on live births may have introduced bias in papers III and IV.

5.3.2 Information bias (misclassification and recall)

In this thesis, information about medication use during pregnancy and many of the sociodemographic factors were self-reported and therefore dependent on the accuracy of reporting and recall of the women. In paper I, some of the participants were new mothers, and hence medication use was retrospectively collected and the possibility of recall bias cannot be ruled out. Questions were indication-oriented in order to enhance recall. A previous study has shown that adopting prompts and indication-oriented questions over open-ended questions has the benefit to improve recall and accuracy in reporting of medication during pregnancy [236]. For papers II-IV, medication use was mostly collected prospectively (Q1 and Q3). Medication use after gestational week 30 and until childbirth was collected retrospectively (Q4) and may be more susceptible to recall bias. The MoBa questionnaires also include indication-oriented questions about medication use to enhance recall. Moreover, as paracetamol and opioid analgesics are medications used intermittently, we cannot rule out the possibility for under-reporting. However, exposure misclassification is likely to be non-differential and could potentially bias the effect estimates towards the null [159]. We do not have information about dose in MoBa. As a proxy of duration of use, we used number of trimesters and number of 4-week intervals.

Some of the outcomes in this thesis were parent-reported and dependent on parents' accuracy in reporting. Most likely a misclassification will be non-differential, however, it may be subject to differential misclassification if there is a difference in how exposed

and unexposed children are followed up after birth or if mothers who have used the medications of interest are more susceptible to report differently than those who have not due to an unmeasured factor. In paper II we had self-reported paracetamol exposure and outcome data from the same source (maternal report), which may make them vulnerable to dependent measurement error. If over-reporting of paracetamol use co-occurs with over-reporting of outcomes, this could produce the appearance of a strong effect of paracetamol on the outcome [100].

5.3.3 Confounding

We used advanced methods in epidemiology to account for confounding in papers II-IV. The MoBa study provided us with a wide range of information about maternal health, sociodemographic and life-style factors that could be potential important confounders. We utilized DAGs to depict the causal relationship between the exposure of interest, the outcome and other variables. Propensity scores were used to account for measured confounders. This is a common method for reducing bias due to indication for medication use in phamacoepidemiological studies [237]. Furthermore, the use of propensity scores substantially reduces the number of covariates in the regression model when there are many potential confounders [237].

In paper II, we included common indications for paracetamol use in our propensity score models (pain, headache/migraine, fever and infections). However, we were not able to account for severity of indication.

In papers III and IV, we chose a slightly different approach. The population was restricted to women reporting an indication for treatment with opioid analgesics (i.e. pain). To further reduce confounding by indication, we included children of mothers with only pre-pregnancy opioid exposure as our reference group. In paper III, we created a variable of number of experienced pain episodes during pregnancy as a proxy of pain severity. However, the questions regarding pain are phrased slightly differently in the MoBa questionnaires.

As many of the confounding factors are time-varying (e.g. pain severity, smoking, alcohol, use of co-medications), the use of a model that could have taken this into account would have strengthen our analysis [238]. Future studies should try to implement this approach.

The role of unmeasured confounding was explored in several ways, including negative control analysis, investigation of treatment effects within different strata of the propensity score, trimming of the propensity score (paper II) and by calculating the e-value (papers II and III). In paper II, all sensitivity analyses indicated that unmeasured

confounding play an important role and we cannot rule out unmeasured confounding as a possible explanation for our findings. However, a limitation of the negative control we used was that we required paracetamol use only prior to pregnancy and no use during pregnancy. This approach condition on future exposure status and could introduce bias [239].

The e-value (2.06 in paper II, and 2.58 in paper III) is the minimum strength of an unmeasured confounder would need to have with both the exposure and the outcome to account for the association [170]. Given the magnitude of the e-values, a single factor may not be able to explain the findings in our studies. However, the combined effects of several smaller confounders should be considered. This points to a limitation of the e-value, as it does not account for combined effects of several unmeasured confounders [226, 240].

5.3.4 Outcome validity

Papers II-IV assess different domains of neurodevelopment and the validity of these outcome measures will be discussed separately.

We used instruments widely recognized within child psychiatry and psychology to assess communication skills [189], behavior [191] and temperament [192] in paper II. These tools show high internal consistency and are strongly predictive of later child diagnosis [188, 191, 194].

The Norwegian version of the Ages and Stages Questionnaire has shown good construct validity [188] and is widely used to detect developmental delay in several domains. In the MoBa Q-5yrs only the communication domain was included, consisting of seven questions regarding the child's language competence. There are six original items and one item that was adapted from the 4-year questionnaire to increase reliability and sensitivity to very low levels of communication skills at 5 years. Cronbach's α was 0.65 in our study.

The Child Behavior Checklist (CBCL/1.5-5) version for preschool children is a widely used and validated measure of children's behavior, and covers a range of emotional, social, and behavioral problems [191]. The CBCL version for older children has been validated in a Norwegian sample [190], whereas the CBCL1.5/5 has been validated in Dutch and Danish samples [241, 242]. The original instrument consists of 100 items describing a behavior exhibited by the child during the last two months. Due to space restrictions, the full version was not included in the MoBa questionnaire. Therefore, specifically selected items that were intended to represent all CBCL subscales, and to

be clinically and theoretically relevant indications of behavior problems were included in the MoBa questionnaire [193]. Cronbach's α can be found in Table B.1.

The Emotionality, Activity and Shyness Temperament Questionnaire (EAS) measures the four temperament dimensions: emotionality (the tendency to become emotionally aroused easily and intensely), activity (preferred activity level), sociability (the tendency to prefer the presence of others to being alone), and shyness (fear of strangers, social inhibition) [192]. The short form of the EAS was used to measure temperament in the MoBa Q-5yrs. The short form has shown to be highly correlated with the original instrument (correlation: 0.92-0.95) [194].

To the best of my knowledge, the validity of an ADHD diagnosis from NPR has not been investigated. However, a study from Denmark, which has a similar healthcare system to Norway, found that a recorded diagnosis of ADHD has a positive predictive value of 0.87 [243]. Not all children with ADHD reach the threshold for a diagnosis; therefore, we also investigated symptoms of ADHD in paper III. ADHD symptoms was measured by the CPRS-R(S) [244], a well-validated instrument [245] that has been shown to predict later ADHD diagnosis [246]. In our sample, we found a good correspondence between ADHD diagnosis and the symptom score.

To the best of my knowledge, there does not exist any "gold standard" on how to measure school performance. The national tests were intended to measure the students' basic skills (or abilities) in reading, numeracy and English with regard to competence goals in the curriculum. They have been evaluated on a yearly basis by the Norwegian Directorate of Education and Training and the tests in reading and numeracy was found to have high reliability (0.86-0.91) [247]. Reading and numeracy skills are dependent on cognitive functions [248], however, these test scores may not be directly correlated with IQ as the results are a product of the child's concentration, knowledge and motivation for the given test [228]. Moreover, scholastic skills can predict future academic achievement, career aptitudes, and socioeconomic status [249, 250].

5.3.5 Sample size and statistical considerations

In paper I, the study sample in most participating European countries was large. But the study samples from Austria, Iceland and The Netherlands were small and the country-specific analysis should be interpreted with caution. Individual countries were grouped into regions in some analyses to facilitate readability of results. However, most analyses were performed based on the total study sample on a woman-level basis.

In paper II, the number of children exposed to paracetamol during pregnancy was large, and there was enough power (80%) to detect a moderately increased risk of the outcomes under study.

In papers III and IV, the proportion of women that used opioid analgesics during pregnancy was approximately 2%, which may limit the statistical power of several analyses. For instance, we were not able to look at individual opioids, nor the difference between weak and strong opioid analgesics. In paper IV, the number of exposed children in the highest duration category were small, thus we might not be able to detect a dose-response-relationship and results should be interpreted with this in mind. Moreover, it was considered important to use multiple imputation to enhance statistical power because 20-30% of the study sample had missing data in important confounders in papers III and IV, respectively.

5.3.6 Generalizability

The data in this thesis was based on data from pregnant women from several European countries (paper I) and Norwegian pregnant women and their children (papers II-IV). The study sample in paper I was more educated that the general birthing population in the individual European countries, which may limit the generalizability within other contexts. The MoBa participants may represent a "healthier" segment of the pregnant population in Norway, which in turn may limit the generalizability of our findings. Furthermore, the oldest MoBa children were born in the late 1990s. Both guidelines for medication use and patterns of use may have changed since then.

5.4 Clinical implications

The research findings from paper I highlight the need for pre-pregnancy counselling in order to optimize medication use during pregnancy, particularly for women with chronic conditions. More research on medication safety in pregnancy is needed to understand the reproductive safety of many medications and to ensure that healthcare professionals and women themselves have access to updated and accurate information.

Prior to prescribing an analgesic for pregnant women, physicians should first consider whether a woman's condition could be treated with non-pharmacological approaches such as physical therapy [52]. The findings from papers II-IV support current guidelines on the use of paracetamol and opioid analgesics in pregnancy. In brief, paracetamol should be used at the lowest effective dose for the shortest possible time. High doses or long-term use of opioid analgesics should be avoided. Overall, findings from the thesis are reassuring for pregnant women that need to use paracetamol or opioid analgesics

for pain management. However, when long-term therapy is needed, pregnant women should consult their physician.

6 Conclusions

This thesis has explored the safety profile of medication used during pregnancy and generated knowledge to achieve a better understanding of the reproductive safety of paracetamol and opioid analgesics on neurodevelopmental outcomes in the offspring.

Results from the thesis research indicate that the majority of European pregnant women used medications classified as safe to use during pregnancy. A considerable proportion of women still used potentially risky medication. Pre-pregnancy counseling is important, particularly for women with chronic conditions, to optimize antenatal prescribing. There is a need to fill the knowledge gap on medication safety in pregnancy. Observational data have been increasingly used and recognized as a valuable source for evidence generation and are becoming more important in regulatory decisions.

Timing of exposure to paracetamol and short term use of paracetamol during pregnancy do not seem to increase the risk of communication, behavioral or temperamental problems in preschool aged children. In addition, we did not find evidence that prenatal exposure to opioid analgesics substantially affected scholastic skills in fifth grade or increased the risk of child ADHD, although a potential duration-effect for ADHD cannot be ruled out. We need more studies to establish a more comprehensive neurodevelopmental safety profile of paracetamol and opioid analgesic use during pregnancy.

Overall, these findings are reassuring and support the recommendations given in the current clinical practice guidelines. Adequate pain management in pregnancy should be discussed on an individual patient level, bearing in mind the benefits and risks of different analgesic therapies.

7 Perspectives

Several advances have been made in recent years to move towards a modern pregnancy pharmacovigilance system [6]. Observational data have been increasingly used and recognized as a valuable source for evidence generation. Abandonment of the FDA pregnancy risk category letter system in favor of narrative statements incorporating real-world safety data into labelling, constitute a crucial step forward [7]. This is essential to ensure that healthcare professionals and the women themselves have access to updated and accurate information. Widespread initiatives and collaborations have been established to monitor and collect information about the safety of medications in pregnancy. For instance, we have the IMI ConcePTION project in Europe [251] and the FDA funded Sentinel System in the U.S. [252]. Further, modern pregnancy pharmacovigilance should also endorse involvement of pregnant women and childbearing-aged women in clinical trials [7]. With use of observational data and international collaborations, combined with the application of advanced epidemiological methods to analyze these data, we may be increasingly equipped to answer important questions about the safety of medications in pregnancy.

Appendices

Appendix A: Introduction

Table A.1 Studies examining the association between prenatal exposure to paracetamol and neurodevelopmental outcomes in children.

Table A.2 Meta-analyses on the association between prenatal exposure to paracetamol and neurodevelopmental outcomes in children.

Table A.1 Studies examining the association between prenatal exposure to paracetamol and neurodevelopmental outcomes in children.

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
Gustavson et al. (2021) [167]	Birth cohort Norway (1999-2008) 26 613	Propensity scores with the following covariates: numbers of indication groups for paracetamol use, birth year, maternal age, alcohol, smoking, symptoms of anxiety and depression, number of co-medications, child sex. Sibling analysis.	Maternal report, 43% exposed.	ADHD diagnosis	Children exposed to paracetamol ≥29 days had increased risk of ADHD (HR: 2.02, 95% CI: 1.17, 3.25). In the sibling control model long-term paracetamol use was association with ADHD at the within-family level (HR: 1.06, 95% CI: 0.51, 2.05).
Baker et al. (2020) [216]	Birth cohort Canada (2007-2009) 345	Inverse probability weighting with propensity scores, with the following covariates child sex, educational status, BMI, smoking, alcohol.	57.7% had detected paracetamol in meconium samples.	ADHD diagnosis. Parent report on a questionnaire or obtained from medical records. Age at assessment: 6-7 years.	Detection of paracetamol in meconium compared to no paracetamol was associated with increased risk of ADHD (OR: 2.43, 95% CI: 1.41, 4.21). Identified a dose-response relationship.
Tovo-Rodrigues et al. (2020) [213]	Birth cohort Brazil (2004) 3624	Regression models adjusted for maternal age, schooling, parity, BMI, smoking, alcohol use, family wealth index, maternal health conditions, use of other analgesics, child sex.	Maternal report, retrospective ascertainment, 28% exposed.	Battelle's Developmental Inventory at 24 months and the Child behavior checklist at 46 months.	Any exposure to paracetamol during gestation was not associated with low neurodevelopmental performance at 24 months or emotional or behavioral problems at 48 months.
Bertoldi et al. (2020) [253]	Cohort study USA (1992-2002) 1217	Maternal age, BMI, education, parity, race/ethnicity, smoking, alcohol, income, child sex, gestational age, birthweight, ibuprofen and antibiotic use.	Maternal report. Any use in 1st and 2nd trimester 41.3%	Cognition assessed with WRAVMA and the Peabody Picture Vocabulary Test Evaluated by trained research assistant Age at assessment 3 years.	Exposure to paracetamol in 1st and 2nd trimester was associated with increased risk of lower drawing score on WRAVMA (β: −1.51, 95% CI: −2.92, −0.10). No associations was found with other outcomes.

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
Bertoldi et al. (2020) [253]	Birth cohort Brazil (2015) 3818	Maternal age, BMI, education, parity, race/ethnicity, smoking, alcohol, income, child sex, ibuprofen and antibiotic use.	Maternal report, 57.6% during 1st or 2nd trimester.	INTER-NDA (domains including language, motor, cognitive and total score). Evaluated by trained interviewers. Child age 2 years.	Exposure to paracetamol in both 1st and 2nd trimester was not associated with INTER-NDA motor scores (β: 0.02, 95% CI: −0.05, 0.09) and was associated with higher INTER-NDA total scores (β: 0.08, 95% CI: 0.01, 0.16).
Rifas-Shiman et al. (2020) [94]	Cohort study USA (1999-2002) 1225	Regression models adjusted for maternal age, education, smoking, parity, household income, child age and sex, race, use of antibiotics, use of antidepressants, EDPS ≥13 in mid-pregnancy.	Maternal report, 46.1% mothers reported using >10 doses.	Parent and teacher reporting on executive function (SDQ and BRIEF) Age at assessment: median 8 years.	Prenatal exposure to paracetamol was associated with lower executive measure.
Liew et al. (2019) [215]	Cohort study USA (1993-2005) 8856	Negative control analysis. Regression models adjusted for maternal age, birth order, child's birth year, maternal chronic disease, use of aspirin and NSAIDs.	Maternal report, 14% used paracetamol regularly during pregnancy.	ADHD diagnosis reported by the mother.	Prenatal exposure to paracetamol was associated with increased risk of ADHD (OR: 1.34, 95% CI: 1.05, 1.72). Exposure 4 years prior and 4 years post pregnancy was not associated with child ADHD.
Chen et al. (2019) [214]	Retrospective study Taiwan (1998-2008) 950 cases, 3800 controls	Regression models adjusted for demographic variables, gestational infections, maternal mental health, comorbid perinatal conditions.	Exposure identified by insurance claims, 68% exposed. Did not capture paracetamol OTC.	ADHD diagnosis.	ADHD risk associated with prenatal paracetamol exposure in 2nd trimester (OR: 1.19, 95% CI: 1.00, 1.40), any trimester (OR: 1.20, 95% CI: 1.01, 1.42), 1st & 2nd trimesters (OR: 1.28, 95% CI: 1.00, 1.64). No dose-response relationship identified.
Golding et al. (2019) [217]	Birth cohort England (1991-1992) 14 062	Exposome analysis to determine factors associated with use of paracetamol, 15 factors selected and included in final regression model.	Maternal report of paracetamol use between week 18 and 32 of pregnancy, 43.9%	Cognitive and behavioral outcomes, assessed by parents and teacher.	Paracetamol exposure between gestational weeks 18-32 was associated with 12 outcomes of hyperactive or attention related behaviors in pre-school aged children.
Ji et al. (2018) [254]	Birth Cohort USA (1998-2016) 1180	Regression models adjusted for maternal age, race/ethnicity, education, smoking, alcohol, BMI, parity, fever, infections, child sex.	Biomarkers of paracetamol in plasma sampled 1-3 days postpartum,	ADHD diagnosis. Median age at diagnosis 7 years. ASD, other	Biomarkers of paracetamol exposure was associated with increased risk of ADHD. 3rd vs 1st tertile: unchanged paracetamol (OR: 2.05, 95% CI: 1.27, 3.32), N-acytl-l-cystein-S-yl

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
			55% had detectable paracetamol.	developmental disabilities.	(OR: 2.03, 95% CI: 1.26, 3.27), paracetamol glucuronide (OR: 2.00, 95% CI: 1.26, 3.18). Dose-response relationship. No association between paracetamol biomarkers and ASD or other developmental disabilities.
Laue et al. (2018) [255]	Cohort study Canada (2007-2009) 118	Regression models adjusted for maternal age, maternal intelligence, BMI, parity, socioeconomic characteristics, child sex.	Paracetamol detected in 53% of the meconium samples.	WISC, with different subtests. Completed by children aged range: 6-8 years	Paracetamol exposure measured in meconium was not statistically significantly associated with decreased scores on any subtests of the WISC. No dose-response detected.
Ruisch et al. (2018) [256]	Birth cohort England 1991-1992 6300	Regression models adjusted for comorbid ADHD, ODD or CD, infections, genetic risk, medication use, life stress, anxiety and depression.	Maternal report, 53% exposed.	Conduct disorder (CD), Oppositional defiant disorder (ODD) 6300 children assessed by maternal rating. 4400 children assessed by teacher rating. Age at assessment: 7 and 9 years.	Prenatal paracetamol exposure was associated with increased risk of ODD on teacher rating (IRR: 1.24, 98.3% CI: 1.05, 1.47). Also associated life stress, smoking, depression. Not associated - maternal infection, aspirin, alcohol.
Tovo-Rodrigues et al. (2018) [220]	Birth cohort Brazil (2004) 4231	Regression models adjusted for child sex, maternal education level and socioeconomic status, maternal age, skin color, parity, smoking, alcohol, infections, self-reported depression/anxiety (yes/no), BMI, use of NSAIDs.	Exposure was retrospectively ascertained. Maternal report (ever/never), 28% exposed.	SDQ reported by parents. Age at assessment: 6 and 11 years.	At 6 years prenatal paracetamol exposure increased boys odds of emotional problems (OR: 1.47, 95% CI: 1.07, 2.02) and hyperactivity/inattention (OR: 1.42, 95% CI: 1.06, 1.92). At 11 years prenatal paracetamol exposure increased boys odds of emotional problems (OR: 1.31, 95% CI: 0.99, 1.73) and hyperactivity/inattention (OR: 1.25, 95% CI: 0.95, 1.65). No associations for girls
Petersen et al. (2018) [257]	Birth cohort Denmark and Norway	Marginal structural models with IPTW. Covariates included maternal occupational status, BMI,	Maternal report, 49% exposed.	Diagnosis of cerebral palsy.	Ever exposure to paracetamol during pregnancy was associated with increased risk of overall cerebral palsy (OR: 1.3, 95% CI: 1.0, 1.7) and

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
	(1996-2002, 1999-2008) 185 617	IVF treatment, smoking, use of other analgesics, infections, birth year.			unilateral spastic cerebral palsy (OR: 1.5, 95% CI: 1.0, 2.2)
Bornehag et al. (2018) [91]	Swedish Environmental Longitudinal, Mother child, Asthma/allergy Sweden (2007-2010) 754	Regression models adjusted for: maternal weight, education, smoking and week of enrollment.	Maternal report from conception until enrollment at GW 8-13 and urine biomarkers, 59% exposed.	Language development assessed by a nurse and parental report. Language delay was defined as use of ≤ 50 words. Age at assessment: 30 months.	Paracetamol use in early pregnancy were associated with increased risk of language delay in girls exposed to > 6 paracetamol tablets vs. 0 tablets (OR: 5.92, 95% CI: 1.10, 31.94) and increased risk of language delay in girls with mothers' urinary paracetamol in highest quartile (OR: 10.34, 95% CI: 1.37, 77.86). No association of paracetamol to language delay in boys.
Gervin et al. (2017) [258]	Subset of the MoBa cohort Norway (1999-2008) 384	DNA methylation analysis. Gene ontology analysis.	Cases: 100% paracetamol biomarkers detected in cord blood / Controls 0%	DNA methylation in children with ADHD.	Children with ADHD and exposed to paracetamol >20 days during gestation had significant differences in DNA methylation compared to controls (no paracetamol, no ADHD).
Ystrom et al. (2017) [95]	Birth cohort Norway (1999-2008) 112 973	Regression models adjusted for familial risk/parent symptoms of ADHD, symptoms of anxiety and depression, alcohol, smoking, BMI, age, parity, education, marital status, indications of use.	Any exposure, by trimester, and duration of use. (Long-term ≥28 days). Maternal report, 47% exposed.	ADHD diagnosis, (child 3-15 years).	Prenatal exposure to paracetamol for >29 days of use was associated with increased risk of ADHD (HR: 2.20, 95% CI: 1.50, 3.24). Number of trimesters with exposure to paracetamol and risk of ADHD; one trimester (HR: 1.07, 95% CI: 0.96, 1.19), two trimesters (HR: 1.22, 95% CI: 1.07, 1.38), three trimesters (HR: 1.27, 95% CI: 0.99, 1.63). Short term use (<8 days) was not associated with increased risk of ADHD.
Avella-Garcia et al. (2016) [88]	Birth cohort Spain (2004-2008) 2644	Regression models adjusted for child gender, age at testing, gestational age at birth, maternal social class, education, maternal	Ever/never use and frequency (never, sporadic, persistent).	Childhood autism spectrum test (CAST), Conners's Kiddie continuous performance test (K-	Children ever exposed to paracetamol during pregnancy had higher risks of hyperactivity/impulsivity (IRR: 1.41, 95% CI: 1.01, 1.98), K-CPT commission errors (IRR: 1.1, 95% CI: 1.03, 1.17), lower detectability

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
		chronic illness, fever or urinary tract infection.	Maternal report, 43% exposed.	CPT), ADHD-DSM-IV form list. Evaluated by teacher and trained psychologist. Age at assessment: 1 and 5 years.	score (β: −0.75, 95% CI: −0.13, −0.02), higher CAST scores in males (β: 0.63, 95% CI: 0.09, 1.18). No information on dose.
Stergiakouli et al. (2016) [97]	Birth cohort England (1991-1992) 7796	Regression models adjusted for age, parity, socioeconomic status, smoking, alcohol, BMI, psychiatric illness, indications of use, polygenic risk score of ADHD.	Exposure at GW 18 and GW 32 Maternal report, 53% exposed.	SDQ. Age at assessment: 7 years.	Prenatal exposure at 32 weeks was associated with increased risk of conduct problems (RR: 1.42, 95% CI: 1.25, 1.62), hyperactivity symptoms (RR: 1.31, 95% CI: 1.16, 1.49), emotional symptoms (RR: 1.29, 95% CI: 1.09, 1.53), total difficulties (RR: 1.46, 95% CI: 1.21, 1.77).
Vlenterie et al. (2016) [96]	Birth cohort Norway (1999-2008) 51 200	Propensity score matching. Variables included maternal age, BMI, parity, marital status, education, smoking, alcohol, symptoms of depression/anxiety, co-medications, health conditions.	Short-term (<28 days) and long-term (≥28 days) use of paracetamol. Maternal report, 40.5% exposed.	Parent reported communication skills, behavior, and temperament. Measured by validated psychometric instruments. Age at assessment: 18 months,	Exposure to paracetamol ≥28 days was associated with increased risk of communication problems (OR: 1.38, 95% CI: 0.98, 1.95) and delayed motor milestone attainment (OR: 1.35, 95% CI: 1.07, 1.70)
Liew et al. (2016) [89]	Birth cohort Denmark (1996-2002) 64 322	Regression models adjusted for: child sex, birth year, maternal age, parity, socioeconomic status, smoking, alcohol, BMI, self-reported psychiatric illness, maternal indications for paracetamol use, use of NSAIDs.	Maternal report in interview, 56% exposed.	ASD diagnosis, Average follow-up 12.7 years.	Any prenatal exposure to paracetamol was associated with increased risk of ASD with HKD symptoms (HR: 1.51, 95% CI: 1.19, 1.92). Dose-response relationship for ASD with HKD. Not associated with other ASD cases (HR: 1.06, 95% CI: 0.92, 1.24).

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
Liew et al. (2016) [93]	Birth cohort Denmark (1996-2002) 1491	Regression models adjusted for: child sex, maternal age, parity, parental education, maternal IQ, smoking, alcohol, indications for paracetamol use, use of NSAIDs.	Maternal report in interview, 59% exposed.	Child IQ assessed by with the WPPSI-R by a trained psychologist. Age at assessment: 5 years.	Prenatal paracetamol use for other than fever was associated with increased risk of lower verbal IQ (2.7 points, 95% CI: –0.19, 5.6) and lower performance IQ (4.3 points, 95% CI: 0.30, 8.3). No IQ change when mothers with fever used paracetamol.
Liew et al. (2016) [92]	Birth cohort Denmark (1996-2002) 1491	Regression models adjusted for maternal age, parental education, BMI, mental health illness, smoking, alcohol, child sex, maternal indication for paracetamol use, NSAIDs use.	Maternal report in interview, 59% exposed.	Attention (TEACH-5). Executive function (BRIEF). Age at assessment: 5 years.	Children prenatally exposed to paracetamol had a higher risk of subnormal overall attention (OR: 1.5, 95% CI: 1.0, 2.5), selective attention (OR: 1.5, 95% CI: 1.0, 2.4) and executive function (OR: 1.5, 95% CI: 0.9, 2.3). Dose-response relationship.
Thompson et al. (2014) [98]	Auckland Birthweight Collaborative Study New Zealand (1995-1997) 871	Regression models adjusted for SGA status, child sex, smoking status, marital status, parity, socioeconomic status, BMI, alcohol, taking medications for psychological conditions.	Maternal report, 50% exposed.	ADHD symptoms, reported by parents and child self-report. SDQ, CPRS-R. Age at assessment: 7, 11.	Children of mothers who used paracetamol during pregnancy had increased risk of higher total difficulties scores and increased risk of ADHD symptoms at 7 and 11 years of age. No risk differences for anti-inflammatories, aspirin, antibiotics, antacids.
Liew et al. (2014) [87]	Birth cohort Denmark (1996-2002) 64 322	Regression models adjusted for age, child sex, child's birth year, gestational age, birth weight, parity, socioeconomic position, smoking, alcohol, BMI, maternal musculoskeletal diseases, fever, inflammation or infection, psychiatric illness, NSAIDs use.	Maternal report in interviews, 56% exposed.	HKD diagnosis, ADHD prescriptions, SDQ at 7 years.	Prenatal paracetamol exposure was associated with increased risk of ADHD diagnosis (HR: 1.37, 95% CI: 1.19, 1.59), ADHD treatment (HR: 1.29, 95% CI: 1.15, 1.44) and ADHD-like behaviors (RR: 1.13, 95% CI: 1.01, 1.27)
Brandlistuen et al. (2013) [72]	Birth cohort Norway (1999-2008) 48 631	Sibling-controlled analysis, regression models adjusted for febrile illness, infections, co-medications.	Short-term (<28 days) and long-term (≥28 days) use of paracetamol.	Communication skills, behavior, and temperament at 3 years.	Exposure to paracetamol >28 days was associated with poor gross motor development (β: 0.24, 95% CI: 0.12, 0.51), poor communication skills (β: 0.20, 95% CI: 0.01, 0.39), increased risk of externalizing (β: 0.28, 95% CI: 0.15, 0.42) and internalizing behavior

Author (year)	Design Country (Study period) Sample size	Method to account for confounding	Exposure ascertainment, prevalence of use during pregnancy	Outcome	Main findings
			Maternal report, 46% exposed.		problems (β: 0.14, 95% CI: 0.01, 0.28) and higher activity levels (β: 0.24, 95% CI: 0.11, 0.38).

ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, Autism Spectrum Disorder; BRIEF, Behavior Ration Inventory of Executive Function; EDPS, Edinburgh Postnatal Depression Scale; MoBa, the Norwegian Mother, Father, and Child Cohort Study; HKD, hyperkinetic disorder; INTER-NDA, Intergrowth-21 Neurodevelopment Assessment; SDQ, strengths and difficulties questionnaire; WISC, Wechsler Intelligence Scale for Children WRAVMA, Wide Range Achievement of visual Motor Abilities.

Table A.2 Meta-analyses on the association between prenatal exposure to paracetamol and neurodevelopmental outcomes in children.

Author (year)	Search criterion	Studies included	Exposure and outcome(s)	Main findings
Masarwa et al. 2018 [259]	MEDLINE, Embase, Cochrane. Inception/January 2017.	7 observational cohort studies including 132 738 mother-child pairs.	Exposure; children exposed to paracetamol during pregnancy. Outcomes: ADHD, ASD and hyperactivity symptoms (3-11 years).	Pooled RR ADHD: 1.34 (95% CI: 1.21-1.47) I^2=72% ASD: 1.19 (95% CI: 1.14-1.25) I^2=14% Hyperactivity symptoms: 1.24 (95% CI: 1.04-1.43) I^2=93%
Gou et al. 2019 [260]	PubMed, Embase, Web of Science, Cochrane. Inception/November 2018.	8 cohort studies including 244 940 mother-child pairs.	Exposure: children exposed to paracetamol during pregnancy compared to non-exposed children. Outcome: ADHD.	Pooled RR ADHD: 1.25 (95% CI: 1.17-1.34) Longer duration of exposure was correlated with a higher risk ratio.
Alemany et al. 2021 [99]	European birth cohorts. Recruitment period: 1991-2008.	6 cohort studies including 73 881 mother-child pairs.	Exposure: children exposed to paracetamol during pregnancy compared to non-exposed children. Outcome: ADHD or ASC symptoms (4-12 years).	OR ADHD symptoms: 1.21 (95% CI: 1.07-1.36) ASC symptoms: 1.19 (95% CI: 1.07-1.33)

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ASC, autism spectrum conditions;

Appendix B: Materials and methods

Table B.1 Description of the parent-reported outcomes used from the MoBa Q-5years (papers II and III).

Table B.2 Overview of variables (papers II-IV).

Table B.1 Description of the parent-reported outcomes used from the MoBa Q-5years (papers II and III).

Outcome	Description	Measure	Cronbach's α
Communication skills	7 items from the communication domain of the Ages and Stages Questionnaire (ASQ) at 5 years, which measures the child's language competence [188, 189].	Dichotomized outcome T-score ≥65 were considered as having clinically relevant communication problems.	0.65
Externalizing behavior	Measured by selected items from the Child Behavior Checklist (CBCL) for preschool children. Consists of several subscales. Items from the subscales; attention problems and aggressive behavior were aggregated into externalizing behavior [190, 191].	Dichotomized outcome T-score ≥63 were considered as having clinically significant externalizing behavior problems.	0.77
Internalizing behavior	Measured by selected items from the Child Behavior Checklist (CBCL) for preschool children. Consists of several subscales. Items from the subscales; emotionally reactive, anxious/depressed and somatic complaints were aggregated into internalizing behavior [190, 191].	Dichotomized outcome T-score ≥63 were considered as having clinically significant externalizing behavior problems.	0.61
Temperament	Assessed by the short version of the Emotional, Activity and Shyness Temperament Questionnaire (EAS), which measures the four temperament dimensions emotionality, activity, sociability, and shyness [192, 193]. All domains consisted of 3 items each.	T-score, analyzed on a continuous scale.	0.70-0.75 according to domain
Symptoms of ADHD	Measured by 12 items from the Conners' Parent Rating Scale Revised Short Form (CPRS-R) which covers areas of inattention and impulsivity/hyperactivity [244, 245].	Z-score, analyzed on a continuous scale. A Z-score of two or more indicate clinically relevant problems with attention and / or hyperactivity.	0.90

ADHD: attention-deficit/hyperactivity disorder; Q: questionnaire.

Table B.2 Overview of variables (papers II-IV).

	MoBa Q1 GW 17	MoBa Q-father	MoBa Q3 GW 30	MBRN Child birth	MoBa Q4 Child age 6 months	NorPD	SSB
Paper II	- Education level - Pre-pregnancy BMI - Folate intake - Smoking habits - Alcohol use - SCL-5 - Co-medications - Chronic conditions		- Use of co-medications - Maternal health conditions - Smoking habits - Alcohol use - SCL-5	- Maternal age - Marital status - Child sex - Birthweight - Prematurity - Malformations	- Use of co-medications - Health conditions - Smoking habits - Alcohol use		
Paper III	- Education level - Income - Pre-pregnancy BMI - Folate intake - Smoking habits - Alcohol use - SCL-5 - Use of co-medications - Illicit drug - Episodes of pain - Chronic conditions	- Age - Education level	- Use of co-medications - Episodes of pain	- Maternal age - Marital status - Parity - Child sex - Malformation, - Prematurity	- Use of co-medications	- Maternal filled prescriptions of ADHD medication - Paternal filled prescriptions of ADHD medication	
Paper IV	- Marital status - Pre-pregnancy BMI - Alcohol use - SCL-5 - Chronic diseases before pregnancy - Use of co-medications			- Maternal age - Parity - Smoking at the beginning of pregnancy - Paternal age - Child sex - Time of year the baby was born			- Maternal education level - Paternal education level - Family income

Co-medications include; anti-epileptics, anti-psychotics, antidepressants, triptanes, NSAIDs, benzodiazepines and benzodiazepine-like drugs, and opioids or paracetamol. Symptoms of anxiety/depression, measured by a short version of the Hopkins Symptom Checklist (SCL-5).

References

[1] Werler, M., et al. "Use of over-the-counter medications during pregnancy". In: *Am J Obstet Gynecol* vol. 193, no. 3 (2005), pp. 771-777.

[2] Daw, J.R., et al. "Prescription drug use during pregnancy in developed countries: A systematic review". In: *Pharmacoepidemiol Drug Saf* vol. 20, no. 9 (2011), pp. 895-902.

[3] Lupattelli, A., et al. "Medication use in pregnancy: A cross-sectional, multinational web-based study". In: *BMJ Open* vol. 4, no. 2 (2014), pp. e004365.

[4] Addis, A., Sharabi, S. and Bonati, M. "Risk classification systems for drug use during pregnancy: Are they a reliable source of information?". In: *Drug Saf* vol. 23, no. 3 (2000), pp. 245-253.

[5] Thorpe, P.G., et al. "Medications in the first trimester of pregnancy: Most common exposures and critical gaps in understanding fetal risk". In: *Pharmacoepidemiol Drug Saf* vol. 22, no. 9 (2013), pp. 1013-1018.

[6] Wood, M., Andrade, S.E. and Toh, S. "Safe expectations: Current state and future directions for medication safety in pregnancy research". In: *Clin Ther* vol. 41, no. 12 (2019), pp. 2467-2476.

[7] Lupattelli, A., Spigset, O. and Nordeng, H. "Learning the effects of psychotropic drugs during pregnancy using real-world safety data: A paradigm shift toward modern pharmacovigilance". In: *Int J Clin Pharm* vol. 40, no. 4 (2018), pp. 783-786.

[8] Bérard, A., et al. "The French pregnancy cohort: Medication use during pregnancy in the French population". In: *PLoS One* vol. 14, no. 7 (2019), pp. e0219095.

[9] Dally, A. "Thalidomide: Was the tragedy preventable?". In: *Lancet* vol. 351, no. 9110 (1998), pp. 1197-1199.

[10] Vargesson, N. "Thalidomide-induced teratogenesis: History and mechanisms". In: *Birth Defects Res C Embryo Today* vol. 105, no. 2 (2015), pp. 140-156.

[11] Herbst, A.L., Ulfelder, H. and Poskanzer, D.C. "Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women". In: *N Engl J Med* vol. 284, no. 15 (1971), pp. 878-881.

[12] EUROmediCAT Steering Group. "EUROmediCAT recommendations for European pharmacovigilance concerning safety of medication use in pregnancy". In: *Pharmacoepidemiol Drug Saf* vol. 24 Suppl 2, (2015), pp. 3-7.

[13] Meador, K.J., et al. "Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): A prospective observational study". In: *Lancet Neurol* vol. 12, no. 3 (2013), pp. 244-252.

[14] Broussard, C.S., et al. "Developing a systematic approach to safer medication use during pregnancy: Summary of a Centers for Disease Control and Prevention--convened meeting". In: *Am J Obstet Gynecol* vol. 211, no. 3 (2014), pp. 208-214.e201.

[15] Horton, D.B., et al. "Research on the effects of medications in pregnancy and in children". In: Strom, B.L., Kimmel, S.E., Hennessy, S. eds. *Pharmacoepidemiology.* 6th edition. Hoboken, NJ: Wiley-Blackwell, 2020, pp. 524-560.

[16] Adam, M.P., Polifka, J.E. and Friedman, J.M. "Evolving knowledge of the teratogenicity of medications in human pregnancy". In: *Am J Med Genet C Semin Med Genet* vol. 157, no. 3 (2011), pp. 175-182.

[17] Lo, W.Y. and Friedman, J.M. "Teratogenicity of recently introduced medications in human pregnancy". In: *Obstet Gynecol* vol. 100, no. 3 (2002), pp. 465-473.

[18] Arlett, P., et al. "Real-world evidence in EU medicines regulation: Enabling use and establishing value". In: *Clin Pharmacol Ther* vol. 111, no. 1 (2022), pp. 21-23.

[19] Lupattelli, A., et al. "Use and intentional avoidance of prescribed medications in pregnancy: A cross-sectional, web-based study among 926 women in Italy". In: *Int J Environ Res Public Health* vol. 17, no. 11 (2020).

[20] Briggs, G.G., Freeman, R.K. and Yaffe, S.J. *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. 10th edition. Philadelphia Wolters Kluwer Health, 2014.

[21] Blalock, S.J., Dickinson, R. and Knapp, P. "Risk evaluation and communication". In: Strom, B.L., Kimmel, S.E., Hennessy, S. eds. *Pharmacoepidemiology.* 6th edition. Hoboken, NJ: Wiley-Blackwell, 2020, pp. 1010-1029.

[22] Chambers, C. "Risk assessment and counseling service available for women with pregnancy exposures to medications". In: *Am J Obstet Gynecol* vol. 195, no. 1 (2006), pp. 334-335.

[23] Läkemedelsindustriföreningen. FASS for vårdpersonal. LINFO Drug Information Ltd. http://www.fass.se/LIF/startpage. (visited on 01.06.2016).

[24] U.S. Food and Drug Administration. FDA online label repository. http://labels.fda.gov/. (visited on 01.06.2016).

[25] Australian Government Department of Health. Australian categorisation system for prescribing medicines in pregnancy. https://www.tga.gov.au/node/4013. Published 2011. (visited on 12.03.2022).

[26] Food and Drug Administration. "Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule". In: *Fed Regist* vol. 79, no. 233 (2014), pp. 72063-72103.

[27] Levy, G. "Pharmacovigilance in pregnancy". In: Doan, T., et al. eds. *Pharmacovigilance: A practical approach.* Missouri: Elsevier, 2019, pp. 113-127.

[28] Hancock, R.L., et al. "The effectiveness of teratology information services (TIS)". In: *Reprod Toxicol* vol. 23, no. 2 (2007), pp. 125-132.

[29] Doering, P.L., Boothby, L.A. and Cheok, M. "Review of pregnancy labeling of prescription drugs: Is the current system adequate to inform of risks?". In: *Am J Obstet Gynecol* vol. 187, no. 2 (2002), pp. 333-339.

[30] Balasch, J. and Gratacós, E. "Delayed childbearing: Effects on fertility and the outcome of pregnancy". In: *Curr Opin Obstet Gynecol* vol. 24, no. 3 (2012), pp. 187-193.

[31] Ayad, M. and Costantine, M.M. "Epidemiology of medications use in pregnancy". In: *Semin Perinatol* vol. 39, no. 7 (2015), pp. 508-511.

[32] Mitchell, A.A., et al. "Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008". In: *Am J Obstet Gynecol* vol. 205, no. 1 (2011), pp. 51-58.

[33] Engeland, A., et al. "Trends in prescription drug use during pregnancy and postpartum in Norway, 2005 to 2015". In: *Pharmacoepidemiol Drug Saf* vol. 27, no. 9 (2018), pp. 995-1004.

[34] Blotière, P.O., et al. "Dispensing of potentially harmful prescription drugs in 1.8 million pregnant women in France: A nationwide study based on two risk classification systems". In: *Drug Saf* vol. 44, no. 12 (2021), pp. 1323-1339.

[35] Raichand, S., et al. "Utilisation of teratogenic medicines before and during pregnancy in Australian women". In: *Aust N Z J Obstet Gynaecol* vol. 60, no. 2 (2020), pp. 218-224.

[36] Trønnes, J.N., Lupattelli, A. and Nordeng, H. "Safety profile of medication used during pregnancy: Results of a multinational European study". In: *Pharmacoepidemiol Drug Saf* vol. 26, no. 7 (2017), pp. 802-811.

[37] Ahmed, S.M., et al. "Self-medication and safety profile of medicines used among pregnant women in a tertiary teaching hospital in Jimma, Ethiopia: A cross-sectional study". In: *Int J Environ Res Public Health* vol. 17, no. 11 (2020).

[38] Donald, S., et al. "Prescription medicines with potential for foetal harm: Dispensing before and during pregnancy in New Zealand, 2005-2015". In: *Eur J Clin Pharmacol* vol. 76, no. 6 (2020), pp. 887-896.

[39] Zhang, J., et al. "Safety of medication use during pregnancy in mainland China: Based on a national health insurance database in 2015". In: *BMC Pregnancy Childbirth* vol. 19, no. 1 (2019), pp. 459.

[40] Rouamba, T., et al. "Safety profile of drug use during pregnancy at peripheral health centres in Burkina Faso: A prospective observational cohort study". In: *Drugs Real World Outcomes* vol. 5, no. 3 (2018), pp. 193-206.

[41] Zomerdijk, I.M., et al. "Dispensing of potentially teratogenic drugs before conception and during pregnancy: A population-based study". In: *Bjog* vol. 122, no. 8 (2015), pp. 1119-1129.

[42] Cleary, B.J., et al. "Medication use in early pregnancy-prevalence and determinants of use in a prospective cohort of women". In: *Pharmacoepidemiol Drug Saf* vol. 19, no. 4 (2010), pp. 408-417.

[43] Kulaga, S., Zagarzadeh, A., Bèrard, A. "Prescriptions filled during pregnancy for drugs with the potential of fetal harm". In: *BJOG* vol. 116, no. 13 (2009), pp. 1788-1795.

[44] Gagne, J.J., et al. "Prescription drug use during pregnancy: A population-based study in regione Emilia-Romagna, Italy". In: *Eur J Clin Pharmacol* vol. 64, no. 11 (2008), pp. 1125-1132.

[45] Andrade, S.E., et al. "Use of prescription medications with a potential for fetal harm among pregnant women". In: *Pharmacoepidemiol Drug Saf* vol. 15, no. 8 (2006), pp. 546-554.

[46] Riley, E.H., et al. "Correlates of prescription drug use during pregnancy". In: *J Womens Health* vol. 14, no. 5 (2005), pp. 401-409.

[47] Schirm, E., et al. "Drug use by pregnant women and comparable non-pregnant women in The Netherlands with reference to the Australian classification system". In: *Eur J Obstet Gynecol Reprod Biol* vol. 114, no. 2 (2004), pp. 182-188.

[48] Malm, H., et al. "Prescription of hazardous drugs during pregnancy". In: *Drug Saf* vol. 27, no. 12 (2004), pp. 899-908.

[49] Mogren, I.M. and Pohjanen, A.I. "Low back pain and pelvic pain during pregnancy: Prevalence and risk factors". In: *Spine (Phila Pa 1976)* vol. 30, no. 8 (2005), pp. 983-991.

[50] Wang, S.M., et al. "Low back pain during pregnancy: Prevalence, risk factors, and outcomes". In: *Obstet Gynecol* vol. 104, no. 1 (2004), pp. 65-70.

[51] Kovacs, F.M., et al. "Prevalence and factors associated with low back pain and pelvic girdle pain during pregnancy: A multicenter study conducted in the Spanish national health service". In: *Spine (Phila Pa 1976)* vol. 37, no. 17 (2012), pp. 1516-1533.

[52] Black, E., et al. "Medication use and pain management in pregnancy: A critical review". In: *Pain Pract* vol. 19, no. 8 (2019), pp. 875-899.

[53] Stovner, L.J., et al. "Epidemiology of headache in Europe". In: *Eur J Neurol* vol. 13, no. 4 (2006), pp. 333-345.

[54] Nezvalova-Henriksen, K., Spigset, O. and Nordeng, H. "Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: A prospective cohort study". In: *BJOG* vol. 120, no. 8 (2013), pp. 948-959.

[55] Kennedy, D. "Analgesics and pain relief in pregnancy and breastfeeding". In: *Aust Prescr* vol. 34, (2011), pp. 10.

[56] Pritham, U.A. and McKay, L. "Safe management of chronic pain in pregnancy in an era of opioid misuse and abuse". In: *J Obstet Gynecol Neonatal Nurs* vol. 43, no. 5 (2014), pp. 554-567.

[57] Bandoli, G., Palmsten, K. and Chambers, C. "Acetaminophen use in pregnancy: Examining prevalence, timing, and indication of use in a prospective birth cohort". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 237-246.

[58] Glover, D.D., et al. "Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population". In: *Am J Obstet Gynecol* vol. 188, no. 4 (2003), pp. 1039-1045.

[59] Kristensen, D.M., et al. "Analgesic use - prevalence, biomonitoring and endocrine and reproductive effects". In: *Nat Rev Endocrinol* vol. 12, no. 7 (2016), pp. 381-393.

[60] Malm, H. and Borisch, C. "Analgesics, non-sterioidal anti-inflammatory drugs (NSAIDs), muscle relaxants and antigout medications". In: Schaefer, C., Peters, P., Miller, R.K. eds. *Drugs during pregnancy and lactation. Treatment options and risk assessment.* . Munich Academic Press Elsevier, 2015, pp. 27-58.

[61] UK Teratology Information Service. Use of non-steroidal anti-inflammatory drugs (NSAIDs) in pregnancy. https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-NON-STEROIDAL-ANTI-INFLAMMATORY-DRUGS-NSAIDS-IN-PREGNANCY/. Published 2019. (visited on 28.02.2022).

[62] U.S. Food and Drug Administration. FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid. https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-avoiding-use-nsaids-pregnancy-20-weeks-or-later-because-they-can-result-low-amniotic. Published 2020. (visited on 28.02.2022).

[63] Källén, K. and Winbladh, B. Acetylsalicylsyre. Fosterpåverkan | Janusmed. . https://janusmed.se/fosterpaverkan. Published 2018. (visited on 28.02.2022).

[64] Bateman, B.T., et al. "Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States". In: *Anesthesiology* vol. 120, no. 5 (2014), pp. 1216-1224.

[65] Desai, R.J., et al. "Increase in prescription opioid use during pregnancy among medicaid-enrolled women". In: *Obstet Gynecol* vol. 123, no. 5 (2014), pp. 997-1002.

[66] Sujan, A.C., et al. "A nation-wide Swedish study of opioid analgesic prescribing patterns during pregnancy and associated preexisting mental health conditions". In: *J Matern Fetal Neonatal Med* (2021 [Online ahead of print] DOI: 10.1080/14767058.2021.1875436).

[67] Wen, X., et al. "Association between prenatal opioid exposure and neurodevelopmental outcomes in early childhood: A retrospective cohort study". In: *Drug Saf* vol. 44, no. 8 (2021), pp. 863-875.

[68] Straub, L., et al. "Trajectories of prescription opioid utilization during pregnancy among pre-pregnancy chronic users and risk of neonatal opioid withdrawal syndrome". In: *Am J Epidemiol* vol. 191, no. 1 (2022), pp. 208-219.

[69] Mahic, M., et al. "In utero opioid exposure and risk of infections in childhood: A multinational Nordic cohort study". In: *Pharmacoepidemiol Drug Saf* vol. 29, no. 12 (2020), pp. 1596-1604.

[70] Chou, R., et al. "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain". In: *J Pain* vol. 10, no. 2 (2009), pp. 113-130.

[71] Den norske legeforening. Retningslinjer for smertelindring. https://www.legeforeningen.no/om-oss/publikasjoner/retningslinjer/retningslinjer-for-smertelindring-2009/. (visited on 26.11.2018).

[72] Brandlistuen, R., et al. "Prenatal paracetamol exposure and child neurodevelopment: A sibling-controlled cohort study". In: *Int J Epidemiol* vol. 42, no. 6 (2013), pp. 1702-1713.

[73] Rubenstein, E., et al. "Brief report: Maternal opioid prescription from preconception through pregnancy and the odds of autism spectrum disorder and autism features in children". In: *J Autism Dev Disord* vol. 49, no. 1 (2019), pp. 376-382.

[74] Liew, Z. and Ernst, A. "Intrauterine exposure to acetaminophen and adverse developmental outcomes: Epidemiological findings and methodological issues". In: *Curr Environ Health Rep* vol. 8, no. 1 (2021), pp. 23-33.

[75] Damkier, P., et al. "Handle with care - interpretation, synthesis and dissemination of data on paracetamol in pregnancy". In: *Nat Rev Endocrinol* vol. 18, no. 3 (2022), pp. 191.

[76] Hjorth, S., et al. "Use and validity of child neurodevelopment outcome measures in studies on prenatal exposure to psychotropic and analgesic medications - a systematic review". In: *PLoS One* vol. 14, no. 7 (2019), pp. e0219778.

[77] Källén, K., et al. Paracetamol. Fosterpåverkan | Janusmed https://janusmed.sll.se/fosterpaverkan?nslIds=IDE4POC2U97HOVERT1. Published 2022. (visited on 19.01.2022).

[78] Organization of Teratology Information Specialists. MotherToBaby. Acetaminophen (paracetamol). https://mothertobaby.org/fact-sheets/acetaminophen-pregnancy/. Published 2020. (visited on 19.01.2022).

[79] Jensen, M.S., et al. "Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism". In: *Epidemiology* vol. 21, no. 6 (2010), pp. 779-785.

[80] Schaefer, C., Peters, P. and Miller, R.K. *Drugs during pregnancy and lactation. Treatment options and risk assessment*. 3rd edition: Academic Press, 2015.

[81] Ghanizadeh, A. "Acetaminophen may mediate oxidative stress and neurotoxicity in autism". In: *Med Hypotheses* vol. 78, no. 2 (2012), pp. 351.

[82] Posadas, I., et al. "Acetaminophen induces apoptosis in rat cortical neurons". In: *PLoS One* vol. 5, no. 12 (2010), pp. e15360.

[83] Frye, C.A., et al. "Endocrine disrupters: A review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems". In: *J Neuroendocrinol* vol. 24, no. 1 (2012), pp. 144-159.

[84] Viberg, H., et al. "Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice". In: *Toxicol Sci* vol. 138, no. 1 (2014), pp. 139-147.

[85] Damkier, P., et al. "Annotations and reflections: Pregnancy and paracetamol: Methodological considerations on the study of associations between in utero exposure to drugs and childhood neurodevelopment". In: *Basic Clin Pharmacol Toxicol* vol. 116, no. 1 (2015), pp. 2-5.

[86] Brandlistuen, R., et al. "Annotations and reflections: Response to "pregnancy and paracetamol: Methodological considerations on the study of associations between in utero exposure to drugs and childhood neurodevelopment"". In: *Basic Clin Pharmacol Toxicol* vol. 116, no. 1 (2015), pp. 6-8.

[87] Liew, Z., et al. "Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders". In: *JAMA Pediatr* vol. 168, no. 4 (2014), pp. 313-320.

[88] Avella-Garcia, C.B., et al. "Acetaminophen use in pregnancy and neurodevelopment: Attention function and autism spectrum symptoms". In: *Int J Epidemiol* vol. 45, no. 6 (2016), pp. 1987-1996.

[89] Liew, Z., et al. "Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study". In: *Autism Research* vol. 9, no. 9 (2016), pp. 951-958.

[90] Bauer, A.Z. and Kriebel, D. "Prenatal and perinatal analgesic exposure and autism: An ecological link". In: *Environ Health* vol. 12, (2013), pp. 41.

[91] Bornehag, C.G., et al. "Prenatal exposure to acetaminophen and children's language development at 30 months". In: *Eur Psychiatry* vol. 51, (2018), pp. 98-103.

[92] Liew, Z., et al. "Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years". In: *Int J Epidemiol* vol. 45, no. 6 (2016), pp. 2009-2017.

[93] Liew, Z., et al. "Prenatal use of acetaminophen and child IQ: A Danish cohort study". In: *Epidemiology* vol. 27, no. 6 (2016), pp. 912-918.

[94] Rifas-Shiman, S.L., et al. "Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 287-298.

[95] Ystrom, E., et al. "Prenatal exposure to acetaminophen and risk of ADHD". In: *Pediatrics* vol. 140, no. 5 (2017), pp. e20163840.

[96] Vlenterie, R., et al. "Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: A propensity score matched cohort study". In: *Int J Epidemiol* vol. 45, no. 6 (2016), pp. 1998-2008.

[97] Stergiakouli, E., Thapar, A. and Davey Smith, G. "Association of acetaminophen use during pregnancy with behavioral problems in childhood: Evidence against confounding". In: *JAMA Pediatr* vol. 170, no. 10 (2016), pp. 964-970.

[98] Thompson, J.M., et al. "Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years". In: *PLoS One* vol. 9, no. 9 (2014), pp. e108210.

[99] Alemany, S., et al. "Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts". In: *Eur J Epidemiol* vol. 36, no. 10 (2021), pp. 993-1004.

[100] Wood, M. "Associations between prenatal acetaminophen exposure and child neurodevelopment: Truth, bias, or a bit of both?". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 233-236.

[101] Bauer, A.Z., et al. "Prenatal paracetamol exposure and child neurodevelopment: A review". In: *Horm Behav* vol. 101, (2018), pp. 125-147.

[102] Talge, N.M. "Prenatal acetaminophen exposure and neurodevelopment: State of the evidence". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 227-229.

[103] Tronnes, J.N., et al. "Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 247-256.

[104] Fewell, Z., Davey Smith, G. and Sterne, J.A. "The impact of residual and unmeasured confounding in epidemiologic studies: A simulation study". In: *Am J Epidemiol* vol. 166, no. 6 (2007), pp. 646-655.

[105] U.S. Food and Drug Administration. FDA has reviewed possible risks of pain medicine use during pregnancy. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy. Published 2015. (visited on 20.01.2022).

[106] Society for Maternal-Fetal Medicine (SMFM) Publications Committee. "Prenatal acetaminophen use and outcomes in children". In: *Am J Obstet Gynecol* vol. 216, no. 3 (2017), pp. B14-b15.

[107] European Medicines Agency. PRAC recommendations on signals. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management/prac-recommendations-safety-signals. (visited on 20.01.2022).

[108] Bauer, A.Z., et al. "Paracetamol use during pregnancy - a call for precautionary action". In: *Nat Rev Endocrinol* vol. 17, no. 12 (2021), pp. 757-766.

[109] Rang, H.P. and Dale, M.M. *Rang and dale's pharmacology*. 6th edition. Edinburgh: Churchill Livingstone Elsevier, 2007.

[110] Yazdy, M.M., Desai, R.J. and Brogly, S.B. "Prescription opioids in pregnancy and birth outcomes: A review of the literature". In: *J Pediatr Genet* vol. 4, no. 2 (2015), pp. 56-70.

[111] Broussard, C.S., et al. "Maternal treatment with opioid analgesics and risk for birth defects". In: *Am J Obstet Gynecol* vol. 204, no. 4 (2011), pp. 314.e311-311.

[112] Bateman, B.T., et al. "Association of first trimester prescription opioid use with congenital malformations in the offspring: Population based cohort study". In: *BMJ* vol. 372, (2021), pp. n102.

[113] Nezvalova-Henriksen, K., Spigset, O. and Nordeng, H. "Effects of codeine on pregnancy outcome: Results from a large population-based cohort study". In: *Eur J Clin Pharmacol* vol. 67, no. 12 (2011), pp. 1253-1261.

[114] Fältmarch, S., et al. "Use of opioids during pregnancy and effects of pregnancy outcomes". In: *Pharmacoepidemiol Drug Saf* vol. 28, no. 9 (2019), pp. 1239-1245.

[115] Brogly, S.B., et al. "Prenatal opioid analgesics and the risk of adverse birth outcomes". In: *Epidemiology* vol. 32, no. 3 (2021), pp. 448-456.

[116] Sujan, A.C., et al. "Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: A population-based study". In: *PLoS Med* vol. 16, no. 12 (2019), pp. e1002980.

[117] Källén, K. and Wide, K.K. Kodein. Fosterpåverkan | Janusmed. https://janusmed.sll.se/fosterpaverkan. Published 2018. (visited on 19.01.2022).

[118] Ross, E.J., et al. "Developmental consequences of fetal exposure to drugs: What we know and what we still must learn". In: *Neuropsychopharmacol* vol. 40, no. 1 (2015), pp. 61-87.

[119] Goldfarb, S.S., et al. "Developmental opioid exposures: Neurobiological underpinnings, behavioral impacts, and policy implications". In: *Exp Biol Med (Maywood)* vol. 245, no. 2 (2020), pp. 131-137.

[120] Boggess, T. and Risher, W.C. "Clinical and basic research investigations into the long-term effects of prenatal opioid exposure on brain development". In: *J Neurosci Res* vol. 100, no. 1 (2022), pp. 396-409.

[121] Vadivelu, N., et al. "The opioid crisis: A comprehensive overview". In: *Curr Pain Headache Rep* vol. 22, no. 3 (2018), pp. 16.

[122] Skovlund, E., et al. "Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids". In: *Pharmacoepidemiol Drug Saf* vol. 26, no. 6 (2017), pp. 625-634.

[123] Azuine, R.E., et al. "Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-income, multiethnic us population". In: *JAMA Netw Open* vol. 2, no. 6 (2019), pp. e196405.

[124] Skovlund, E., et al. "In utero exposure to analgesic opioids and language development in 5-year old children". In: *Pharmacoepidemiol Drug Saf* vol. 29, no. 6 (2020), pp. 736-744.

[125] Strom, B.L. "What is pharmacoepidemiology?". In: Strom, B.L., Kimmel, S.E., Hennessy, S. eds. *Pharmacoepidemiology.* 6th edition. Hoboken, NJ: Wiley-Blackwell, 2020, pp. 3-26.

[126] Hernán, M. and Robins, J.M. "Using big data to emulate a target trial when a randomized trial is not available". In: *Am J Epidemiol* vol. 183, no. 8 (2016), pp. 758-764.

[127] Rothman, K. *Epidemiology an introduction* 2nd edition. New York: Oxford University Press, 2012.

[128] Huybrechts, K.F., Bateman, B.T. and Hernández-Díaz, S. "Use of real-world evidence from healthcare utilization data to evaluate drug safety during pregnancy". In: *Pharmacoepidemiol Drug Saf* vol. 28, no. 7 (2019), pp. 906-922.

[129] Etminan, M. and Samii, A. "Pharmacoepidemiology i: A review of pharmacoepidemiologic study designs". In: *Pharmacotherapy* vol. 24, no. 8 (2004), pp. 964-969.

[130] Rothman, K. and Greenland, S. "Cohort studies". In: Rothman, K., Greenland, S., Lash, T.L. eds. *Modern epidemiology.* 3rd edition. Philadelphia: Lippincott Wiliams & Wilkins, 2008, pp. 100-110.

[131] Strom, B.L. "Choosing among the available data sources for pharmacoepidemiologic research". In: Strom, B.L., Kimmel, S.E., Hennessy, S. eds. *Pharmacoepidemiology* 6th edition. Hoboken, NJ: Wiley Blackwell, 2020, pp. 357-374.

[132] Nilsen, R.M., et al. "Self-selection and bias in a large prospective pregnancy cohort in Norway". In: *Paediatr Perinat Epidemiol* vol. 23, no. 6 (2009), pp. 597-608.

[133] Olsen, J., et al. "The Danish national birth cohort--its background, structure and aim". In: *Scand J Public Health* vol. 29, no. 4 (2001), pp. 300-307.

[134] Magnus, P., et al. "Cohort profile update: The Norwegian Mother and Child Cohort study (MoBa)". In: *Int J Epidemiol* vol. 45, no. 2 (2016), pp. 382-388.

[135] Werler, M., et al. "Reporting accuracy among mothers of malformed and nonmalformed infants". In: *Am J Epidemiol* vol. 129, no. 2 (1989), pp. 415-421.

[136] Mills, J.L., et al. "The absence of a relation between the periconceptional use of vitamins and neural-tube defects. National institute of child health and human development neural tube defects study group". In: *N Engl J Med* vol. 321, no. 7 (1989), pp. 430-435.

[137] Lieff, S., et al. "Selection bias and the use of controls with malformations in case-control studies of birth defects". In: *Epidemiology* vol. 10, no. 3 (1999), pp. 238-241.

[138] Palmsten, K., et al. "The most commonly dispensed prescription medications among pregnant women enrolled in the U.S. Medicaid program". In: *Obstet Gynecol* vol. 126, no. 3 (2015), pp. 465-473.

[139] Rothman, K., Greenland, S. and Lash, T.L. "Types of epidemiologic studies". In: Rothman, K., Greenland, S., Lash, T.L. eds. *Modern epidemiology.* Philadelphia: Lippincott Williams & Wilkins, 2008, pp. 87-99.

[140] Andrade, S.E., et al. "Administrative claims data versus augmented pregnancy data for the study of pharmaceutical treatments in pregnancy". In: *Curr Epidemiol Rep* vol. 4, no. 2 (2017), pp. 106-116.

[141] Larsen, P.S., et al. "Pregnancy and birth cohort resources in Europe: A large opportunity for aetiological child health research". In: *Paediatr Perinat Epidemiol* vol. 27, no. 4 (2013), pp. 393-414.

[142] van Gelder, M., Bretveld, R.W. and Roeleveld, N. "Web-based questionnaires: The future in epidemiology?". In: *Am J Epidemiol* vol. 172, no. 11 (2010), pp. 1292-1298.

[143] O'Higgins, A., et al. "The use of digital media by women using the maternity services in a developed country". In: *Ir Med J* vol. 107, no. 10 (2014), pp. 313-315.

[144] van Gelder, M., et al. "The PRIDE study: Evaluation of online methods of data collection". In: *Paediatr Perinat Epidemiol* vol. 34, no. 5 (2020), pp. 484-494.

[145] van Gelder, M., et al. "Web-based questionnaires to assess perinatal outcome proved to be valid". In: *J Clin Epidemiol* vol. 90, (2017), pp. 136-143.

[146] van Gelder, M., et al. "Using web-based questionnaires to assess medication use during pregnancy: A validation study in 2 prospectively enrolled cohorts". In: *Am J Epidemiol* vol. 187, no. 2 (2018), pp. 326-336.

[147] Irgens, L.M. "The medical birth registry of Norway; a source for epidemiological and clinical research". In: *Scand J Rheumatol Suppl* vol. 107, (1998), pp. 105-108.

[148] Bliddal, M., et al. "The Danish medical birth register". In: *Eur J Epidemiol* vol. 33, no. 1 (2018), pp. 27-36.

[149] Benevent, J., et al. "Pharmacoepidemiology in pregnancy". In: *Therapie* vol. 74, no. 2 (2019), pp. 289-300.

[150] Cohen, J.M., et al. "Agreement between paternal self-reported medication use and records from a national prescription database". In: *Pharmacoepidemiol Drug Saf* vol. 27, no. 4 (2018), pp. 413-421.

[151] Skurtveit, S., et al. "Self-reported data on medicine use in the Norwegian Mother and Child Cohort study compared to data from the Norwegian prescription database". In: *Norsk Epidemiologi* vol. 24, no. 1-2 (2014), pp. 209-216.

[152] Laursen, M., et al. "Comparison of electronic self-reported prescription medication use during pregnancy with the national prescription register in Denmark". In: *Pharmacoepidemiol Drug Saf* vol. 29, no. 3 (2020), pp. 328-336.

[153] Lash, T.L., et al. "Good practices for quantitative bias analysis". In: *Int J Epidemiol* vol. 43, no. 6 (2014), pp. 1969-1985.

[154] Wood, M., et al. "Longitudinal methods for modeling exposures in pharmacoepidemiologic studies in pregnancy". In: *Epidemiol Rev* vol. 43, no. 1 (2022), pp. 130-146.

[155] Bromley, R.L. and Baker, G.A. "Fetal antiepileptic drug exposure and cognitive outcomes". In: *Seizure* vol. 44, (2017), pp. 225-231.

[156] Cuthbert, B.N. and Insel, T.R. "Toward the future of psychiatric diagnosis: The seven pillars of RDoC". In: *BMC Medicine* vol. 11, (2013), pp. 126.

[157] Nordeng, H., Lupattelli, A. and Wood, M. "Prenatal exposure to antidepressants and increased risk of psychiatric disorders". In: *BMJ* vol. 358, (2017), pp. j3950.

[158] Rothman, K. *Epidemiology an introduction*. 2nd edition. New York: Oxford University Press, 2012.

[159] Rothman, K., Greenland, S. and Lash, T.L. "Validity in epidemiological studies". In: Rothman, K., Greenland, S., Lash, T.L. eds. *Modern epidemiology.* 3rd edition. Philadelphia: Lippincott Williams & Wilkins 2008, pp. 128-147.

[160] Wood, M., et al. "Making fair comparisons in pregnancy medication safety studies: An overview of advanced methods for confounding control". In: *Pharmacoepidemiol Drug Saf* vol. 27, no. 2 (2018), pp. 140-147.

[161] Lund, J.L., Richardson, D.B. and Stürmer, T. "The active comparator, new user study design in pharmacoepidemiology: Historical foundations and contemporary application". In: *Curr Epidemiol Rep* vol. 2, no. 4 (2015), pp. 221-228.

[162] Shrier, I. and Platt, R.W. "Reducing bias through directed acyclic graphs". In: *BMC Med Res Methodol* vol. 8, (2008).

[163] Bandoli, G., et al. "Constructing causal diagrams for common perinatal outcomes: Benefits, limitations and motivating examples with maternal antidepressant use in pregnancy". In: *Paediatr Perinat Epidemiol* vol. 30, no. 5 (2016), pp. 521-528.

[164] Stürmer, T., et al. "Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs". In: *J Intern Med* vol. 275, no. 6 (2014), pp. 570-580.

[165] Schneeweiss, S. and Suissa, S. "Advanced approaches to controlling confounding in pharmacoepidemiologic studies". In: Strom, B.L., Kimmel, S.E., Hennessy, S. eds. *Pharmacoepidemiology.* Hoboken, NJ: Wiley-Blackwell, 2020, pp. 1078-1108.

[166] Austin, P.C. "An introduction to propensity score methods for reducing the effects of confounding in observational studies". In: *Multivar Behav Res* vol. 46, no. 3 (2011), pp. 399-424.

[167] Gustavson, K., et al. "Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder - a longitudinal sibling control study". In: *JCPP Advances* vol. 1, no. 2 (2021), pp. e12020.

[168] Lipsitch, M., Tchetgen, E.T. and Cohen, T. "Negative controls: A tool for detecting confounding and bias in observational studies". In: *Epidemiology* vol. 21, no. 3 (2010), pp. 383-388.

[169] VanderWeele, T.J. and Ding, P. "Sensitivity analysis in observational research: Introducing the e-value". In: *Ann Intern Med* vol. 167, no. 4 (2017), pp. 268-274.

[170] Ding, P. and VanderWeele, T.J. "Sensitivity analysis without assumptions". In: *Epidemiology* vol. 27, no. 3 (2016), pp. 368-377.

[171] Hernán, M. and Robins, J.M. *Causal inference: What if.* Boca Raton: Chapman & Hall/CRC, 2020.

[172] Hernán, M., et al. "Observational studies analyzed like randomized experiments: An application to postmenopausal hormone therapy and coronary heart disease". In: *Epidemiology* vol. 19, no. 6 (2008), pp. 766-779.

[173] Lupattelli, A., Wood, M. and Nordeng, H. "Analyzing missing data in perinatal pharmacoepidemiology research: Methodological considerations to limit the risk of bias". In: *Clin Ther* vol. 41, no. 12 (2019), pp. 2477-2487.

[174] Graham, J.W. "Missing data analysis: Making it work in the real world". In: *Annu Rev Psychol* vol. 60, (2009), pp. 549-576.

[175] Sterne, J.A., et al. "Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls". In: *BMJ* vol. 338, (2009), pp. b2393.

[176] White, I.R., Royston, P. and Wood, A.M. "Multiple imputation using chained equations: Issues and guidance for practice". In: *Stat Med* vol. 30, no. 4 (2011), pp. 377-399.

[177] Perkins, N.J., et al. "Principled approaches to missing data in epidemiologic studies". In: *Am J Epidemiol* vol. 187, no. 3 (2018), pp. 568-575.

[178] Rothman, K., et al. "Causation and causal inference". In: Rothman, K., Greenland, S., Lash, T.L. eds. *Modern epidemiology.* Philadelphia: Lippincott Williams & Wilkins, 2008, pp. 5-31.

[179] Vandenbroucke, J.P., Broadbent, A. and Pearce, N. "Causality and causal inference in epidemiology: The need for a pluralistic approach". In: *Int J Epidemiol* vol. 45, no. 6 (2016), pp. 1776-1786.

[180] Hill, A.B. "The environment and disease: Association or causation?". In: *Proc R Soc Med* vol. 58, no. 5 (1965), pp. 295-300.

[181] Shepard, T.H. ""Proof" of human teratogenicity". In: *Teratology* vol. 50, no. 2 (1994), pp. 97-98.

[182] Wilcox, A.J. "Birth defects". In: *Fertility and pregnancy: An epidemiologic perspective.* . 1st edition. New York: Oxford University Press, 2010, pp. 230-245.

[183] Andersen, S.L. "Trajectories of brain development: Point of vulnerability or window of opportunity?". In: *Neurosci Biobehav Rev* vol. 27, no. 1-2 (2003), pp. 3-18.

[184] Norwegian Institue of Public Health. Questionnaires from MoBa. https://www.fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/. Published 2005. Updated 17.12.2021. (visited on 12.03.2022).

[185] Helsedirektoratet. Beskrivelse av innhold i NPR. https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr/innhold-og-kvalitet-i-npr. Published 2019. (visited on 12.03.2022).

[186] Norwegian Institute of Public Health. Norwegian prescription database (NorPD) Available from https://www.fhi.no/en/hn/health-registries/norpd/. Published 2019. (visited on 10.11.2020).

[187] WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index https://www.whocc.no/atc_ddd_index/. (visited on 12.03.2022).

[188] Richter, J. and Janson, H. "A validation study of the Norwegian version of the Ages and Stages Questionnaires". In: *Acta Paediatr* vol. 96, no. 5 (2007), pp. 748-752.

[189] Squires, J., Bricker, D. and Potter, L. "Revision of a parent-completed development screening tool: Ages and Stages Questionnaires". In: *J Pediatr Psychol* vol. 22, no. 3 (1997), pp. 313-328.

[190] Novik, T.S. "Validity of the Child Behaviour Checklist in a Norwegian sample". In: *Eur Child Adolesc Psychiatry* vol. 8, no. 4 (1999), pp. 247-254.

[191] Achenbach, T.M. and Ruffle, T.M. "The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies". In: *Pediatr Rev* vol. 21, no. 8 (2000), pp. 265-271.

[192] Buss, A.H. and Plomin, R. *Temperament: Early developing personality traits*. Hillsdale, NJ: Lawrence Erlbaum Associates Inc, 1984.

[193] Tambs, K. and Røysamb, E. "Selection of questions to short-form versions of original psychometric instruments in MoBa". In: *Norsk Epidemiologi* vol. 24, no. 1-2 (2014), pp. 195-201.

[194] Mathiesen, K., Tambs, K. . "The EAS temperament questionnaire - factor structure, age trends, reliability, and stability in a Norwegian sample". In: *J Child Psychol Psychiatry* vol. 40, (1999), pp. 431-439.

[195] The Norwegian Directorate for Education and Training. Kva er nasjonale prøver? . https://www.udir.no/eksamen-og-prover/prover/nasjonale-prover/om-nasjonale-prover/. Updated 20.11.2019. (visited on 12.11.2021).

[196] Bursac, Z., et al. "Purposeful selection of variables in logistic regression". In: *Source Code Biol Med* vol. 3, (2008).

[197] Greenland, S., Pearl, J. and Robins, J.M. "Causal diagrams for epidemiologic research". In: *Epidemiology* vol. 10, no. 1 (1999), pp. 37-48.

[198] Textor, J., Hardt, J. and Knüppel, S. "Dagitty: A graphical tool for analyzing causal diagrams". In: *Epidemiology* vol. 22, no. 5 (2011), pp. 745.

[199] Glymour, M., Greenland, S. "Causal diagrams". In: Rothman, K., Greenland, S., Lash, T.L. eds. *Modern epidemiology*. Third edition. Philadelphia: Lippincott Williams & Wilkins, 2008, pp. 183-209.

[200] Brookhart, M.A., et al. "Variable selection for propensity score models". In: *Am J Epidemiol* vol. 163, no. 12 (2006), pp. 1149-1156.

[201] Austin, P.C. and Stuart, E.A. "Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies". In: *Stat Med* vol. 34, no. 28 (2015), pp. 3661-3679.

[202] Harder, V.S., Stuart, E.A. and Anthony, J.C. "Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research". In: *Psychol Methods* vol. 15, no. 3 (2010), pp. 234-249.

[203] White, I.R. and Royston, P. "Imputing missing covariate values for the cox model". In: *Stat Med* vol. 28, no. 15 (2009), pp. 1982-1998.

[204] Hardin, J.W. and Hilbe, J.M. *Generalized estimating equations*. Boca Raton: CRC Press, 2013.

[205] Leyrat, C., et al. "Propensity score analysis with partially observed covariates: How should multiple imputation be used?". In: *Stat Methods Med Res* vol. 28, no. 1 (2019), pp. 3-19.

[206] Mitra, R. and Reiter, J.P. "A comparison of two methods of estimating propensity scores after multiple imputation". In: *Stat Methods Med Res* vol. 25, no. 1 (2016), pp. 188-204.

[207] Nordeng, H. "Drug utilization in pregnant women". In: Elseviers, M., et al. eds. *Drug utilization research: Methods and applications.* Chichester: Wiley-Blackwell, 2016, pp. 240-247.

[208] Yang, T., et al. "Maternal characteristics associated with pregnancy exposure to FDA category C, D, and X drugs in a Canadian population". In: *Pharmacoepidemiol Drug Saf* vol. 17, no. 3 (2008), pp. 270-277.

[209] Nordeng, H., Koren, G. and Einarson, A. "Pregnant women's beliefs about medications-a study among 866 Norwegian women". In: *Ann Pharmacother* vol. 44, no. 9 (2010), pp. 1478-1484.

[210] Ystrom, E., Vollrath, M.E. and Nordeng, H. "Effects of personality on use of medications, alcohol, and cigarettes during pregnancy". In: *Eur J Clin Pharmacol* vol. 68, no. 5 (2012), pp. 845-851.

[211] Sannerstedt, R., et al. "Drugs during pregnancy: An issue of risk classification and information to prescribers". In: *Drug Saf* vol. 14, no. 2 (1996), pp. 69-77.

[212] de Fays, L., et al. "Use of paracetamol during pregnancy and child neurological development". In: *Dev Med Child Neurol* vol. 57, no. 8 (2015), pp. 718-724.

[213] Tovo-Rodrigues, L., et al. "Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children

exposed to acetaminophen during foetal development". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 278-286.

[214] Chen, M.H., et al. "Prenatal exposure to acetaminophen and the risk of attention-deficit/hyperactivity disorder: A nationwide study in Taiwan". In: *J Clin Psychiatry* vol. 80, no. 5 (2019), pp. 18m12612.

[215] Liew, Z., et al. "Use of negative control exposure analysis to evaluate confounding: An example of acetaminophen exposure and attention-deficit/hyperactivity disorder in nurses' health study II". In: *Am J Epidemiol* vol. 188, no. 4 (2019), pp. 768-775.

[216] Baker, B.H., et al. "Association of prenatal acetaminophen exposure measured in meconium with risk of attention-deficit/hyperactivity disorder mediated by frontoparietal network brain connectivity". In: *JAMA Pediatr* vol. 174, no. 11 (2020), pp. 1073-1081.

[217] Golding, J., et al. "Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 257-266.

[218] Inoue, K., et al. "Behavioral problems at age 11 years after prenatal and postnatal exposure to acetaminophen: Parent-reported and self-reported outcomes". In: *Am J Epidemiol* vol. 190, no. 6 (2021), pp. 1009-1020.

[219] Parker, S.E., Collett, B.R. and Werler, M. "Maternal acetaminophen use during pregnancy and childhood behavioural problems: Discrepancies between mother- and teacher-reported outcomes". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 299-308.

[220] Tovo-Rodrigues, L., et al. "Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort". In: *BMC Psychiatry* vol. 18, no. 1 (2018).

[221] Polanczyk, G., et al. "The worldwide prevalence of ADHD: A systematic review and metaregression analysis". In: *Am J Psychiatry* vol. 164, no. 6 (2007), pp. 942-948.

[222] Masarwa, R., Platt, R.W. and Filion, K.B. "Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias?". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 309-317.

[223] Kurth, T., et al. "Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect". In: *Am J Epidemiol* vol. 163, no. 3 (2006), pp. 262-270.

[224] Damkier, P. "Simple twist of fate: In utero exposure to acetaminophen and risk of childhood attention deficit hyperactivity disorder". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 230-232.

[225] Alwan, S., et al. "Paracetamol use in pregnancy - caution over causal inference from available data". In: *Nat Rev Endocrinol* vol. 18, no. 3 (2022), pp. 190.

[226] Leppert, B., et al. "Association of maternal neurodevelopmental risk alleles with early-life exposures". In: *JAMA Psychiatry* vol. 76, no. 8 (2019), pp. 834-842.

[227] Elkjær, L.S., et al. "Association between prenatal valproate exposure and performance on standardized language and mathematics tests in school-aged children". In: *JAMA Neurol* vol. 75, no. 6 (2018), pp. 663-671.

[228] Christensen, J., et al. "Association of maternal antidepressant prescription during pregnancy with standardized test scores of Danish school-aged children". In: *JAMA* vol. 326, no. 17 (2021), pp. 1725-1735.

[229] Brogly, S. "Maternal and child health after prenatal opioid exposure". In: *JAMA Netw Open* vol. 2, no. 6 (2019), pp. e196428.

[230] Wang, M.V., et al. "Co-occurring development of early childhood communication and motor skills: Results from a population-based longitudinal study". In: *Child Care Health Dev* vol. 40, no. 1 (2014), pp. 77-84.

[231] Young, A.R., et al. "Young adult academic outcomes in a longitudinal sample of early identified language impaired and control children". In: *J Child Psychol Psychiatry* vol. 43, no. 5 (2002), pp. 635-645.

[232] Vejrup, K., Magnus, P. and Magnus, M. "Lost to follow-up in the Norwegian Mother, Father and Child Cohort Study". In: *Paediatr Perinat Epidemiol* vol. 36, no. 2 (2022), pp. 300-309.

[233] Biele, G., et al. "Bias from self selection and loss to follow-up in prospective cohort studies". In: *Eur J Epidemiol* vol. 34, no. 10 (2019), pp. 927-938.

[234] Liew, Z., et al. "Bias from conditioning on live birth in pregnancy cohorts: An illustration based on neurodevelopment in children after prenatal exposure to organic pollutants". In: *Int J Epidemiol* vol. 44, no. 1 (2015), pp. 345-354.

[235] Werler, M. and Parker, S.E. "Bias from conditioning on live-births in pregnancy cohorts: An illustration based on neurodevelopment in children after prenatal exposure to organic pollutants ". In: *Int J Epidemiol* vol. 44, no. 3 (2015), pp. 1079-1080.

[236] de Jong-van den Berg, L.T., et al. "Drug use in pregnancy: A comparative appraisal of data collecting methods". In: *Eur J Clin Pharmacol* vol. 45, no. 1 (1993), pp. 9-14.

[237] Glynn, R.J., Schneeweiss, S. and Stürmer, T. "Indications for propensity scores and review of their use in pharmacoepidemiology". In: *Basic Clin Pharmacol Toxicol* vol. 98, no. 3 (2006), pp. 253-259.

[238] Robins, J.M., Hernán, M. and Brumback, B. "Marginal structural models and causal inference in epidemiology". In: *Epidemiology* vol. 11, no. 5 (2000), pp. 550-560.

[239] Lund, J.L., et al. "Conditioning on future exposure to define study cohorts can induce bias: The case of low-dose acetylsalicylic acid and risk of major bleeding". In: *Clin Epidemiol* vol. 9, (2017), pp. 611-626.

[240] Hjorth, S. "*Childhood outcomes after prenatal exposure to analgesics or antibiotics"* PhD Thesis. Department of Pharmacy, University of Oslo; 2021.

[241] Koot, H.M., et al. "Behavioral and emotional problems in young preschoolers: Cross-cultural testing of the validity of the Child Behavior Checklist/2-3". In: *J Abnorm Child Psychol* vol. 25, no. 3 (1997), pp. 183-196.

[242] Kristensen, S., Henriksen, T.B. and Bilenberg, N. "The Child Behavior Checklist for ages 1.5-5 (CBCL/1(1/2)-5): Assessment and analysis of parent- and caregiver-reported problems in a population-based sample of Danish preschool children". In: *Nord J Psychiatry* vol. 64, no. 3 (2010), pp. 203-209.

[243] Mohr-Jensen, C., et al. "The validity and reliability of the diagnosis of hyperkinetic disorders in the Danish psychiatric central research registry". In: *Eur Psychiatry* vol. 35, (2016), pp. 16-24.

[244] Conners, C.K., et al. "The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity". In: *J Abnorm Child Psychol* vol. 26, no. 4 (1998), pp. 257-268.

[245] Kumar, G. and Steer, R.A. "Factorial validity of the Conners' Parent Rating Scale-revised: Short form with psychiatric outpatients". In: *J Pers Assess* vol. 80, no. 3 (2003), pp. 252-259.

[246] Oerbeck, B., et al. "Early predictors of ADHD: Evidence from a prospective birth cohort". In: *J Atten Disord* vol. 24, no. 12 (2020), pp. 1685-1692.

[247] Utdanningsdirektoratet. Nasjonale prøver 2013 - fagmiljøenes analyse av prøvene. https://www.udir.no/tall-og-forskning/finn-forskning/rapporter/nasjonale-prover-2013---fagmiljoenes-analyse-av-provene/. Updated 04.02.2016. (visited on 03.02.2022).

[248] Titz, C. and Karbach, J. "Working memory and executive functions: Effects of training on academic achievement". In: *Psychol Res* vol. 78, no. 6 (2014), pp. 852-868.

[249] Duncan, G.J., et al. "School readiness and later achievement". In: *Dev Psychol* vol. 43, no. 6 (2007), pp. 1428-1446.

[250] Ritchie, S.J. and Bates, T.C. "Enduring links from childhood mathematics and reading achievement to adult socioeconomic status". In: *Psychol Sci* vol. 24, no. 7 (2013), pp. 1301-1308.

[251] Thurin, N.H., et al. "From inception to ConcePTION: Genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding". In: *Clin Pharmacol Ther* vol. 111, no. 1 (2022), pp. 321-331.

[252] Ball, R., et al. "The FDA's sentinel initiative--a comprehensive approach to medical product surveillance". In: *Clin Pharmacol Ther* vol. 99, no. 3 (2016), pp. 265-268.

[253] Bertoldi, A.D., et al. "Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood". In: *Paediatr Perinat Epidemiol* vol. 34, no. 3 (2020), pp. 267-277.

[254] Ji, Y., et al. "Maternal biomarkers of acetaminophen use and offspring attention deficit hyperactivity disorder". In: *Brain Sciences* vol. 8, no. 7 (2018), pp. 127.

[255] Laue, H.E., et al. "Association between meconium acetaminophen and childhood neurocognitive development in GESTE, a Canadian cohort study". In: *Toxicol Sci* vol. 167, no. 1 (2019), pp. 138-144.

[256] Ruisch, I.H., et al. "Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the Avon Longitudinal Study of Parents and Children". In: *J Psychiatr Res* vol. 101, (2018), pp. 63-71.

[257] Petersen, T.G., et al. "Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child". In: *Int J Epidemiol* vol. 47, no. 1 (2018), pp. 121-130.

[258] Gervin, K., et al. "Long-term prenatal exposure to paracetamol is associated with DNA methylation differences in children diagnosed with ADHD". In: *Clin Epigenetics* vol. 9, (2017), pp. 77.

[259] Masarwa, R., et al. "Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: A systematic review, meta-analysis, and meta-regression analysis of cohort studies". In: *Am J Epidemiol* vol. 187, no. 8 (2018), pp. 1817-1827.

[260] Gou, X., et al. "Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis". In: *Aust N Z J Psychiatry* vol. 53, no. 3 (2019), pp. 195-206.

Papers

I

Paper I

Safety profile of medication used during pregnancy: results of a multinational European study

Johanne N. Trønnes, Angela Lupattelli, Hedvig Nordeng

Pharmacoepidemiol Drug Saf vol. 26, no. 7 (2017)
pp. 802-811. DOI: 10.1002/pds.4213.

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 802–811
Published online 27 April 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4213

ORIGINAL REPORT

Safety profile of medication used during pregnancy: results of a multinational European study†

Johanne N. Trønnes[1]*, Angela Lupattelli[1] and Hedvig Nordeng[1,2]

[1] *PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway*
[2] *Department of Child Health, Norwegian Institute of Public Health, Oslo, Norway*

ABSTRACT

Purpose The present study describes the safety profile of medications used during pregnancy across European countries and examines maternal factors associated with the use of risky medications during pregnancy.
Methods This study is based on a multinational, web-based study conducted in 15 European countries from October 2011 to February 2012. Information about maternal demographics, illnesses, and medication use during pregnancy was collected via an electronic questionnaire. Pregnant women and new mothers with a child less than 1-year-old could participate. The Swedish, Australian, and U.S. risk classification systems were used to evaluate medication safety. Descriptive statistics and generalized estimating equation models were used.
Results A total of 587 medications were reported by the study sample (n = 6657). Sixty-nine percent of the women used medications classified as safe, 28% used medications classified as risky, and 3% used medications with no classification available. Both socio-demographic and medical factors were associated with the use of risky medications during pregnancy. Having a chronic disorder was the factor with the strongest association with the use of risky medications during pregnancy (adjusted odds ratio = 3.99, 95% confidence interval 3.54–4.49).
Conclusions The majority of women used medications classified as safe to use during pregnancy. However, a considerable proportion of women still used medications classified as risky. Having a chronic disorder was an important driver for using risky medications. Such use may still be appropriate when considering the woman's underlying condition. Pre-pregnancy counselling is important to ensure safe medication use for both mother and child. © 2017 The Authors. *Pharmacoepidemiology & Drug Safety* Published by John Wiley & Sons Ltd.

KEY WORDS—medication; pregnancy; risk classification; multinational; pharmacoepidemiology

Received 1 July 2016; Revised 17 February 2017; Accepted 21 March 2017

INTRODUCTION

Recent studies have reported that medication use is common among pregnant women.[1–4] Up to 80% of women are estimated to use at least one medication, over-the-counter (OTC) or prescribed, during pregnancy.[4] Taking a medication during pregnancy involves weighing the risk versus benefits for both mother and child. Avoiding required treatment for maternal illnesses, such as diabetes, epilepsy, hypertension, or infections, may endanger both the mother and child. On the other hand, unnecessary medication use during pregnancy can have potential negative consequences for the fetus.[5,6] Different risk classification systems have been established to provide guidance to healthcare professionals when counselling pregnant women on the safety of medications during pregnancy. The most well-known risk classification systems are from Sweden, Australia, and the U.S. and place medications in risk groups according to fetal safety.[7] Although the risk classification systems have limitations,[8–10] they are of great value when describing medication utilization patterns at an aggregated level.

Studies have consistently reported the use of potentially risky medications during pregnancy, with prevalence estimates of 2% in Italy,[11] 19% in Denmark,[12] 21% in the Netherlands,[13] and 59% in France.[14] The variation may be attributed to

*Correspondence to: J. N. Trønnes, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Postbox 1068, Blindern, 0316 Oslo, Norway. E-mail: j.n.tronnes@farmasi.uio.no

†This work was presented as a poster at the 32nd ICPE Conference in Dublin, Ireland, August 2016.

differences in the study methods used to assess medication exposure, the classification system used, and the type of medications assessed, making comparisons of results almost impossible.[1] Uniform collection of data on medication utilization during pregnancy across countries may overcome some of these drawbacks. Moreover, multinational studies of the safety profiles of medications used during pregnancy are lacking. As medication utilization patterns may change over time, such use needs to be continuously monitored in order to identify potentially risky practices during pregnancy and to ensure safe medication use for both mother and child.

To the best of our knowledge, no previous study has uniformly evaluated the safety profile of medications taken by pregnant women across several European countries. The purpose of this study was to describe the safety profile of medications used during pregnancy across European countries and to examine maternal factors associated with the use of potentially risky medications during pregnancy.

METHODS

Study design, population, and data collection

This is a sub-study of "The Multinational Medication Use in Pregnancy Study", a web-based study conducted in countries in Eastern, Northern, and Western Europe, North and South America, and Australia to investigate medication use during pregnancy with a focus on maternal attitudes, perception of risk, and mental well-being.[4] For the present study, we only included women residing in European countries at the time the questionnaire was completed (i.e., Austria, Croatia, Finland, France, Iceland, Italy, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, the Netherlands, and UK). Both pregnant women and new mothers with a child less than 1 year of age could participate. The study recruited women through placement of banners (invitations to participate in the study) on national websites and/or social networks commonly visited by pregnant women and new mothers. The survey questionnaire was administered by Questback (http://www.questback.com). The online questionnaire was accessible for a period of 2 months in each participating country between October 1, 2011, and February 29, 2012. The baseline characteristics of the study population were compared on an individual country level with those of the potential general birthing or childbearing population in the same country. Reports from National Statistics Bureaus or previous national studies were utilized for this purpose. The sample was found to be representative with respect to age, parity, and smoking habits.[4] However, the sample comprised a group of women with higher education than the general birthing population in each country. A detailed description of the study was published previously.[4]

Medication use report

The most common short-term/acute illnesses and the most prevalent chronic disorders were listed in the questionnaire, and women were asked if they suffered/had suffered from these conditions during pregnancy. In the case of a positive answer, women could report any medication use according to indication as a free-text entry. The questionnaire also included five questions about the use of OTC medications, with examples of branded product names in the various countries to enhance recall. Timing of exposure was requested when medication use occurred; the options were gestational weeks 0–12 (first trimester), weeks 13–24 (second trimester), and 25 weeks to delivery (third trimester).[4] All medications were then coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the fifth (substance) level in accordance with the World Health Organization ATC index.[15] The use of iron, mineral supplements, vitamins, and herbal remedies was excluded from this analysis.

Safety classification of medications

We used internationally recognized risk classification systems to place each medication in risk groups according to fetal safety.

The Swedish classification system (Farmaceutiska Spesialiteter i Sverige [FASS])[16] was used as the primary source because it is relevant for medications on the European market and reflects international text book recommendations better than the U.S. classification system from the Food and Drug Administration (FDA).[7,17] In general, when medications were part of a combination, they were classified according to the main substance (e.g., the medication meclozine and combinations were classified according to meclozine). Medications consisting of components with different risk classifications were classified according to the component with the highest risk. If the medication had no risk classification and was a topical formulation, but the substance had a classification for the oral formulation, the medication was conservatively classified. Whenever the medication risk classification was lacking in FASS, the Australian classification system was used as a

DOI: 10.1002/pds

secondary source.[18] If neither of these classification systems was able to classify the medication, the FDA system was used as a tertiary source.[19,20] The rationale for using two additional risk classification systems was to classify as many medications as possible. Medications that could not be classified by any of these resources were considered as "not classified".

All three risk classification systems place medications in risk groups according to fetal safety. FASS is based on clinical and/or animal data and consists of four different groups (A to D). Group A includes the safest medications; group B includes medications with undetermined risk and classified based on animal data, with allocation to three subgroups (B1, B2, and B3); and groups C and D include medications that may involve risk to the fetus or an increased risk of fetal damage.[8] The FDA categorization also uses letters from A to D, with an additional X category for medications that have been shown to be teratogenic.[8] The Australian classification system is an extrapolation of both of the other systems.[8]

Medications were grouped as "probably safe" or "potentially risky" in order to facilitate the analysis and to make categories of more clinical interest. The "probably safe" group consisted of FASS and Australian categories A, B1, and B2 and FDA categories A and B, and the "potentially risky" group consisted of FASS and Australian categories B3, C, and D, Australian category X, and FDA categories C, D, and X. In a woman-level analysis, women using multiple medications were assigned to the group with the highest risk.

Statistical analysis

Descriptive statistics were used as appropriate. Factors associated with the use of potentially risky medications during pregnancy (dichotomous variable: potentially risky medication user versus probably safe medication user) were examined using the generalized estimating equations (GEE) with a binomial distribution.[21] GEE were used in order to account for any clustering on region of residence. Data are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). A two-tailed p-value < 0.05 was considered significant. Candidate variables in a univariate model with $p < 0.25$ were selected for inclusion in the multivariate GEE model. Variables with $p > 0.05$ or $< 20\%$ impact on the beta coefficients of the retained variables were removed from the multivariate model. The final multivariate model included significant independent variables: education level, employment status, parity, folic acid use before and during pregnancy, alcohol consumption, smoking, and chronic disorders.

In a set of sensitivity analyses, women using unclassified medications were grouped together with (i) the probably safe medication users and (ii) the potentially risky medication users. We also restricted the medication pattern analysis to women with an overview of the entire pregnancy (i.e., pregnant women in third trimester and new mothers). A sensitivity analysis excluding all topical formulations was also performed. Country-specific analyses investigating associations between maternal factors and potentially risky medications were performed using logistic regression. We adjusted for the same covariates as in the main analysis. All statistical analyses were performed using STATA/MP 14.1 for Windows (StataCorp LP, TX, USA).

RESULTS

A total of 9615 women replied to the informed consent question after reading the study description, and 9483 (98.6%) confirmed their willingness to participate in the study and completed the online questionnaire. Women with unknown country of residence and women from non-European countries were excluded, leaving 8363 eligible women. We excluded an additional 1576 (18.8%) non-users of medication and 130 (1.6%) women with unspecified medication use, leaving 6657 (79.6%) women with specified medication use as our study sample (Figure 1). The study sample had higher parity and consumed more alcohol after awareness of pregnancy than the non-users of medication. Our study sample included women from Western (n = 2543), Northern (n = 2355), and Eastern Europe (n = 1759). A total of 3455 (51.9%) women were pregnant at the time they completed the questionnaire, and 3202 (48.1%) had delivered their babies within the previous year. The socio-demographic and lifestyle factors of the study sample are summarized in Table 1.

Classification and use of medications during pregnancy

A total of 587 different medications were used by the study sample and classified according to the three risk classification systems (Figure 2).

Using the combined classification method, 223 (38.0%) of the 587 medications were classified

DOI: 10.1002/pds

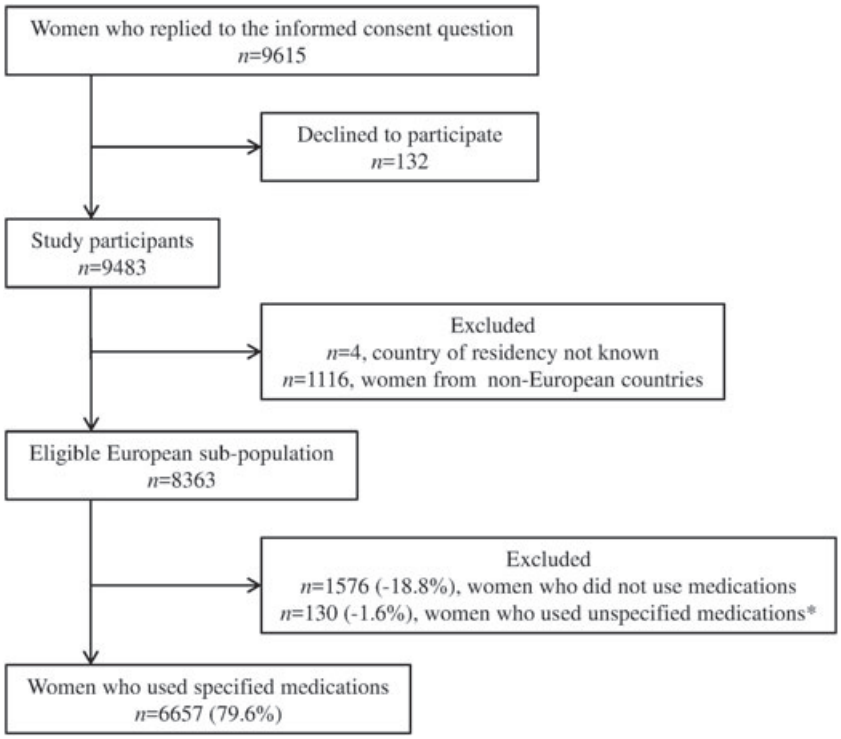


Figure 1. Participant flowchart.*Women with unspecified medication use only provided a general response, such as "antibiotics" or that they could not remember, when asked about medication use and were excluded from the analysis

as probably safe to use during pregnancy. Probably safe medications were used by 4596 (69.0%) women, most commonly paracetamol (acetaminophen), ordinary salt combinations, and alginic acid.

A total of 228 (38.8%) medications were classified as potentially risky to use during pregnancy and were used by 1881 (28.3%) women. The most frequent medications in this group were ibuprofen, metoclopramide, and codeine (combined products excluding neuroleptics).

No classification was available for 136 (23.2%) medications, which were used by 180 (2.7%) of the women. The most frequent medications in this group were drotaverine, hydrotalcite, and combinatory nasal preparations. Table 2 shows the 10 most frequently used medications classified as probably safe, potentially risky, and unclassified, respectively.

Regardless of trimester, the majority of women used medications classified as probably safe (Table S1). A sensitivity analysis including only women with an overview of the entire pregnancy did not find major differences in the percentage of women using medication in the different safety groups according to trimester of use.

Medication use according to country/region of residence

The majority of women across all countries used medications that are safe to use during pregnancy. A higher proportion of women from Northern Europe used medications that are potentially risky during pregnancy compared with women from the other regions. The highest proportion of women using unclassified medications were from Eastern Europe (Figure 3). Table S2 shows the most common potentially risky and unclassified medications according to region.

Factors associated with the use of potentially risky medications during pregnancy

Several factors were associated with the use of potentially risky medications during pregnancy, as summarized in Table 3. Being a student, a housewife, or working as healthcare personnel, having previous children, not using folic acid, consuming alcohol, and smoking were associated with the use of potentially risky medications during pregnancy, and the magnitude of the associations ranged between 10% and 30% increased odds. Having a chronic disorder was the factor with the

DOI: 10.1002/pds

Table 1. Maternal socio-demographic and lifestyle factors among the study sample

Maternal characteristics	Women who used specified medication (n_{total} = 6657) *n* (%)	Women who used probably safe medication (*n* = 4596) *n* (%)	Women who used potentially risky medication (*n* = 1881) *n* (%)	Women who used unclassified medication (*n* = 180) *n* (%)
Region of residence				
Western Europe*	2543 (38.2)	1875 (40.8)	625 (33.2)	43 (23.9)
Northern Europe†	2355 (35.4)	1605 (34.9)	743 (39.5)	7 (3.9)
Eastern Europe‡	1759 (26.4)	1116 (24.3)	513 (27.3)	130 (72.2)
Maternal age (years)				
≤20	195 (2.9)	129 (2.8)	58 (3.1)	8 (10.0)
21–30	3656 (54.9)	2513 (54.7)	1032 (54.9)	111 (61.7)
31–40	2672 (40.2)	1859 (40.4)	752 (40.0)	61 (33.9)
≥41	134 (2.0)	95 (2.1)	39 (2.1)	0 (0.0)
Marital status				
Married/cohabitant	6332 (95.1)	4390 (95.5)	1774 (94.3)	168 (93.3)
Single/divorced/other	325 (4.9)	206 (4.5)	107 (5.7)	12 (6.7)
Education level				
Less than high school	314 (4.7)	201 (4.4)	106 (5.6)	7 (3.9)
High school	1887 (28.4)	1343 (29.2)	505 (26.9)	39 (21.7)
More than high school	3672 (55.2)	2517 (54.8)	1036 (55.1)	119 (66.1)
Other, unspecified	784 (11.7)	535 (11.6)	234 (12.4)	15 (8.3)
Working status				
Student	587 (8.8)	382 (8.3)	191 (10.2)	14 (7.8)
Housewife	538 (8.1)	347 (7.6)	174 (9.3)	17 (9.4)
Healthcare personnel	941 (14.1)	625 (13.6)	303 (16.2)	13 (7.2)
Employed in other sector	3964 (59.5)	2801 (60.9)	1044 (55.5)	119 (66.1)
Job seeker	288 (4.3)	204 (4.4)	74 (3.9)	10 (5.6)
None	331 (5.0)	231 (5.0)	93 (4.9)	7 (3.9)
Previous children				
Yes	3380 (50.8)	2299 (50.0)	1009 (53.6)	72 (40.0)
No	3277 (49.2)	2297 (50.0)	872 (46.4)	108 (60.0)
Planned pregnancy				
Yes, not completely unexpected	6062 (91.1)	4203 (91.4)	1691 (89.9)	168 (93.3)
No, it was not planned	574 (8.6)	380 (8.3)	182 (9.7)	12 (6.7)
Folic acid use				
Yes	6100 (91.6)	4241 (92.3)	1694 (90.1)	165 (91.7)
No	503 (7.6)	324 (7.0)	166 (8.8)	13 (7.2)
Alcohol consumption after known pregnancy				
Yes	1149 (17.3)	750 (16.3)	358 (19.0)	41 (22.8)
No	5457 (82.0)	3816 (83.0)	1506 (80.1)	135 (75.0)
Smoking during pregnancy				
Yes	621 (9.3)	394 (8.6)	205 (10.9)	22 (12.2)
No	6022 (90.5)	4197 (91.3)	1667 (88.6)	158 (87.8)

Numbers may not add up to total number due to missing values. For *folic acid* use and *alcohol consumption during pregnancy*, the response "cannot remember" was treated as a missing value. Missing values are less than 5% of the total.
When a woman used multiple medications, she was assigned to the group with highest risk.
*Western Europe includes Austria, France, Italy, Switzerland, the Netherlands, and UK.
†Northern Europe includes Finland, Iceland, Norway, and Sweden.
‡Eastern Europe includes Croatia, Poland, Russia, Serbia, and Slovenia.

strongest association with the use of potentially risky medications during pregnancy (aOR = 3.99, 95% CI 3.54–4.49).

In the country-specific analyses, maternal chronic disorder was consistently one of the most important factors associated with the use of potentially risky medication during pregnancy. The magnitude of this association across countries was generally similar to that observed in the main analysis, although stronger in the UK (aOR = 7.6, 95% CI 5.2–10.9) and weaker in Russia (aOR = 1.4, 95% CI 1.0–1.9). We observed more common use of potentially risky medications among women using alcohol during pregnancy in some of the Eastern European countries compared with non-drinkers. Similarly, women with previous children (in France, Norway, UK, Sweden, and Russia) or working as healthcare professionals (in Norway, France, Poland, and UK) were more likely to use potentially risky medication than nulliparous women or women employed in a non-health-related sector, respectively.

DOI: 10.1002/pds

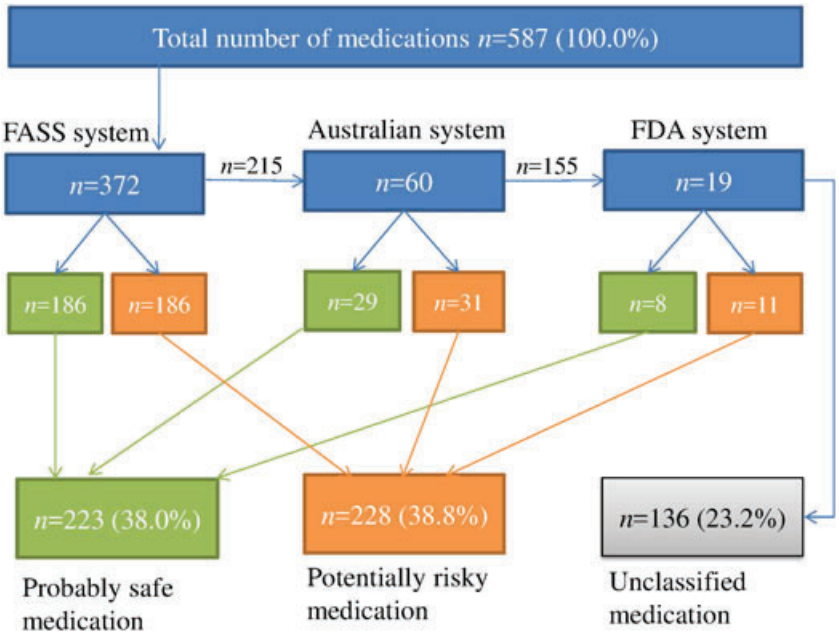


Figure 2. Flowchart of how the medications were evaluated and classified according to three internationally recognized risk classification systems. FASS, Farmaceutiska Spesialiteter i Sverige; FDA, Food and Drug Administration. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2. Top 10 probably safe, potentially risky, and unclassified medications used during pregnancy

Probably safe medications (ATC code)	*n* (%)	Potentially risky medications (ATC code)	*n* (%)	Unclassified medications (ATC code)	*n* (%)
Paracetamol (acetaminophen) (N02BE01)	4459 (67.0)	Ibuprofen (M01AE01)	309 (4.6)	Drotaverine (A03AD02)	153 (2.3)
Ordinary salt combinations (A02AD01)	1424 (21.4)	Metoclopramide (A03FA01)	230 (3.5)	Hydrotalcite (A02AD04)	93 (1.4)
Alginic acid (A02BX13)	1194 (17.9)	Codeine combinations (N02AA59)	178 (2.7)	Nasal preparations, combinations (R01AX30)	77 (1.2)
Xylometazoline (R01AA07)	787 (11.8)	Acetylsalicylic acid combinations (N02BA51)	96 (1.4)	Glycerol (enema) (A06AG04)	60 (0.9)
Lactulose (A06AD11)	514 (7.7)	Naphazoline (R01AA08)	72 (1.1)	Throat preparations, antiseptics, various (R02AA20)	58 (0.9)
Oxymetazoline (R01AA05)	459 (6.9)	Mometasone (R01AD09)	65 (1.0)	Calcium carbonate (A02AC01)	49 (0.7)
Levothyroxine (H03AA01)	328 (4.9)	Econazole (G01AF05)	54 (0.8)	Phloroglucinol (A03AX12)	47 (0.7)
Meclozine (R06AE05)	257 (3.9)	Formoterol and budesonide (R03AK07)	54 (0.8)	Fusafungine (R02AB03)	47 (0.7)
Amoxicillin (J01CA04)	200 (3.0)	Interferon alpha-2b (L03AB05)	52 (0.8)	Magaldrate (A02AD02)	45 (0.7)
Salbutamol (R03AC02)	166 (2.5)	Sertraline (N06AB06)	48 (0.7)	Glycerol (A06AX01)	42 (0.6)

Women may have used more than one medication.
Study sample, *n* = 6657.

In a sub-analysis of individual chronic disorders (i.e., allergy, asthma, anxiety, depression, cardiovascular disease, hypothyroidism, and rheumatic illness), all except hypothyroidism were significantly associated with the use of potentially risky medications (Table S3).

In sensitivity analyses, we found no difference from the main analysis when unclassified medication

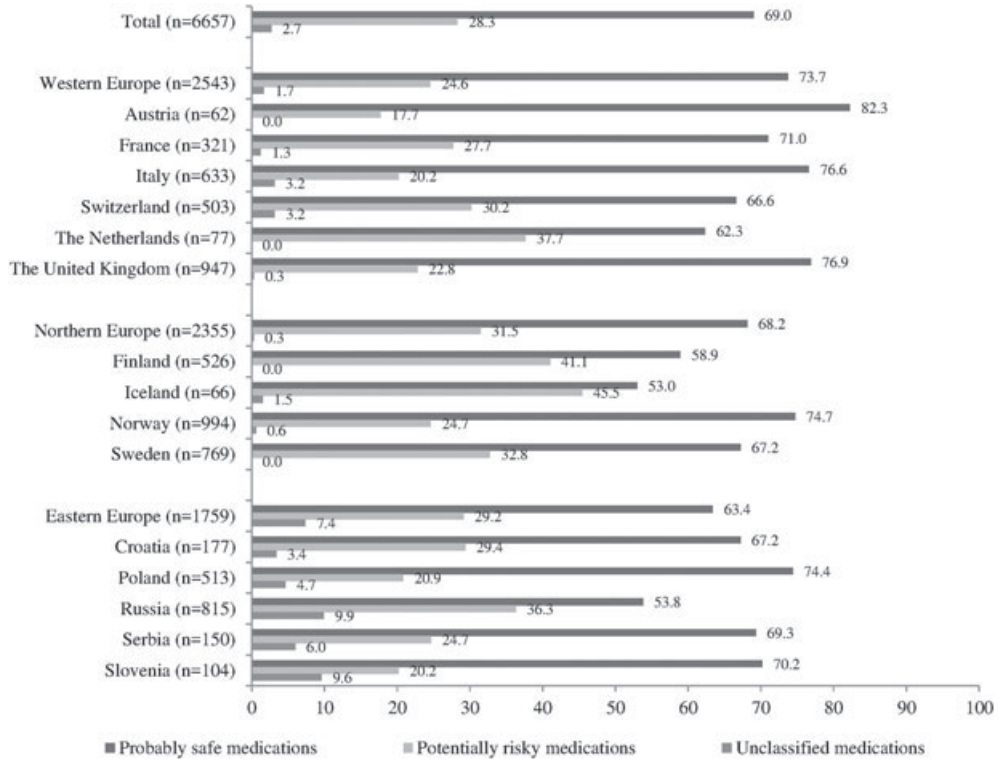


Figure 3. The proportion of women (%) using probably safe, potentially risky, and unclassified medications during pregnancy according to region and country of residence. When a woman used multiple medications, she was assigned to the group with highest risk

users were grouped together with the probably safe medication users. When grouping the unclassified medication users with the potentially risky medication users, smoking and higher parity were not associated with the use of potentially risky medications.

Sensitivity analyses excluding topical formulations did not produce material differences in the results from the main analysis.

DISCUSSION

To the best of our knowledge, this study is the first to examine the safety profile of medications used during pregnancy and maternal factors associated with potentially risky medication use during pregnancy across several European countries. It is reassuring that the majority of women used medications classified as safe to use during pregnancy. However, 28% of the women used potentially risky medications, which is in line with findings from previous studies.[1] In addition, one-fifth of the medications could not be classified, even after using three different risk classification systems. Not surprisingly, the Summary of Product Characteristics for most unclassified medications could not fill this knowledge gap because it had limited or no information available in the pregnancy section. A medication utilization study by Olesen *et al.*[12] was also unable to classify 12% of the prescriptions used by pregnant women in Denmark. Taken together, the findings indicate that many medications used by pregnant women have inadequate safety information available and that studies of medication safety during pregnancy are urgently needed.

Differences in medication use between regions/countries with respect to safety classification may be explained by different health needs of the pregnant population and differences in preconception counselling or pregnancy planning in the individual countries.

The most commonly used medications classified as risky were ibuprofen, metoclopramide, and codeine, which were mainly used among women in Western and Northern Europe. Classification of these medications as potentially risky is related to the risks of premature closure of the *ductus arteriosus* after use in the third trimester,[22] conflicting data on teratogenicity,[23] and perinatal complications after use in the third trimester,[22] respectively. Many of the potentially risky medications are used during pregnancy when safer alternatives are not available

DOI: 10.1002/pds

Table 3. Factors associated with use of potentially risky medications during pregnancy

Maternal characteristics	OR (95% CI)	Adjusted OR (95% CI)
Age (as continuous variable)	1.01 (0.99–1.02)	—
Marital status		
Married or cohabiting	Reference	—
Single/divorced/other	1.29 (1.01–1.63)	—
Education level		
Less than high school	1.40 (1.08–1.81)	1.20 (0.91–1.58)
High school	Reference	Reference
More than high school	1.07 (0.94–1.21)	1.10 (0.96–1.27)
Other	1.19 (0.99–1.43)	1.23 (1.01–1.50)
Working status		
Student	1.25 (1.03–1.51)	1.33 (1.09–1.63)
Housewife	1.40 (1.15–1.70)	1.29 (1.04–1.59)
HCP	1.28 (1.09–1.49)	1.31 (1.11–1.54)
Employed in other sector	Reference	Reference
Job seeker	0.97 (0.74–1.28)	0.92 (0.68–1.23)
None	1.08 (0.84–1.39)	0.93 (0.71–1.21)
Previous children		
Yes	1.13 (1.02–1.26)	1.14 (1.02–1.28)
No	Reference	Reference
Planned pregnancy		
Yes, not completely unexpected	Reference	—
No, it was not planned	1.21 (1.01–1.46)	—
Folic acid use before and/or during pregnancy		
Yes	Reference	Reference
No	1.26 (1.04–1.53)	1.26 (1.02–1.55)
Alcohol use after awareness of pregnancy		
Yes	1.28 (1.11–1.47)	1.29 (1.11–1.50)
No	Reference	Reference
Smoking during pregnancy		
Yes	1.30 (1.09–1.56)	1.30 (1.07–1.59)
No	Reference	Reference
Acute illness		
Yes	0.96 (0.46–1.99)	—
No	Reference	—
Chronic disorder		
Yes	3.93 (3.49–4.42)	3.99 (3.54–4.49)
No	Reference	Reference

The outcome variable is categorized as *using potentially risky medications* (1) and *using probably safe medications* (0). For *folic acid use* and *alcohol consumption*, the response "cannot remember" was treated as a missing value.
OR, odds ratio; CI, confidence interval; HCP, healthcare personnel.

or switching of medications is not recommended. Individual benefit–risk evaluations for mother and child have to be taken into consideration. Avoiding all potentially risky medications during pregnancy is unrealistic because some conditions require treatment, and the woman's medical history and disease severity must be taken into account.[5]

Interestingly, the highest proportion of women using unclassified medications was among women from Russia. This could be due to multiple factors: (i) many of the medications used in Eastern Europe may not be on the market in Northern Europe, U.S., or Australia and may lack a classification in the three reference systems used in the current study; and (ii) medication safety studies during pregnancy have so far focused on common exposures in the Western countries, causing a broader knowledge gap for medications used in other parts of the world. However, our findings at the country level should be interpreted with caution because of the small sample sizes in some of the countries.

Having a chronic disorder was the strongest predictor of the use of potentially risky medications during pregnancy. Women with a chronic disorder had an almost fourfold increased odds of using potentially risky medications compared with women without these conditions. Little information is available on which and to what extent maternal characteristics are associated with exposure to potentially "risky" medications. Previous studies[24,25] have reported that pregnant women with a chronic health condition are more likely to use medications with potential risks than women without these conditions. However, our study provided novel insights into the role of individual chronic disorders on the use of potentially risky medication during pregnancy. Among the individual chronic disorders, we found that anxiety and depression had the strongest association with the use of potentially risky medications during pregnancy.

Chronic conditions often require treatment and, even though safer alternatives may be available, switching medication is not always recommended. Switching medications can cause relapse in well-adjusted patients and increase the risk to the fetus. The importance of pre-pregnancy counselling should be emphasized to optimize antenatal prescribing, especially for conditions in which switching medication is not recommended.

The main strengths of this study include the uniform collection of data regarding medication use during pregnancy across several European countries. The use of a web-based recruitment strategy enabled us to reach a wide segment of the birthing population. An invitation to participate in the study was placed on websites frequently visited by pregnant women in the countries of interest, and an online questionnaire may be appropriate for women of childbearing age residing in countries with high Internet access. However, we cannot rule out the possibility of self-selection bias because respondents were women who had Internet access, happened to visit the actual website(s), and decided to participate in the study. However, recent

epidemiological studies indicate the validity of web-based recruitment methods.[26,27] In addition, women may answer more truthfully in an online questionnaire than in a face-to-face interview. The questionnaire comprised several questions on medication use based on timing and indication for use, and included information on OTC medications.

One limitation of the study was that information about medication use was self-reported and, thus, dependent on the women's reporting and recall. Therefore, an underestimation of medication use cannot be excluded. In addition, a risk of poorer recall cannot be ruled out for new mothers because data were recorded retrospectively. However, as shown previously,[4] this has only deflated the prevalence of short-term medication use, but not the use of chronic medications. Furthermore, our results depend on the classification system used, as they differ with respect to the allocation of drugs to risk categories. Addis *et al.*[8] compared these three classification systems and found that only 26% of the medications common to all three systems were placed in the same risk factor categories. Moreover, the FDA recently ruled to replace the current letter-based classification system with three detailed narrative subsections that provide explanations based on available information about the potential benefits and risks for the mother, fetus, and breastfeeding child.[28] Finally, this study was limited to describing medication utilization patterns during pregnancy and cannot evaluate the appropriateness of the medication use of the individual pregnant women. Our results should be interpreted with these strengths and limitations in mind.

CONCLUSION

It is reassuring that the majority of women across several European countries used medications classified as safe to use during pregnancy. However, a considerable proportion of women still used potentially risky medications. Both socio-demographic and medical conditions were associated with the use of potentially risky medications during pregnancy. However, such use may still be appropriate when considering the woman's underlying condition. Therefore, pre-pregnancy counselling is important to ensure safe medication use for both mother and child.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- The majority of women used medications classified as safe to use during pregnancy.
- Twenty-eight percent of the women used medications classified as potentially risky.
- Regional differences were observed with respect to the use of medications in different risk groups.
- One out of five medications used by the women lacked a classification in the risk classification systems.
- Both socio-demographic and medical factors were associated with the use of potentially risky medications during pregnancy.

ETHICS STATEMENT

All participants provided informed consent by answering "Yes" to the question, "Are you willing to participate in the study?". The South-East Regional Ethics Committee in Norway approved the study. Ethical approval or notification of the relevant national ethics boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

ACKNOWLEDGEMENTS

We thank the Steering Committee of OTIS and ENTIS for reviewing the study protocol of the "Multinational Medication Use in Pregnancy Study" and all website providers who contributed to the recruitment phase. We are also grateful to all of the women who took part in this study and the national study coordinators (Spigset O., Twigg M. J., Zagorodnikova K., Mårdby A. C., Moretti M. E., Drozd M., Panchaud A., Hameen-Anttila K., Rieutord A., Gjergja Juraski R., Odalovic M., Kennedy D., Rudolf G., Passier J. L. M., Juch H., and Björnsdóttir I.).

"The Multinational Medication Use in Pregnancy Study" was supported by the Foundation for Promotion of Norwegian Pharmacies. This work was supported by the Norwegian Pharmaceutical Society. J. N. T.'s doctoral work and A. L.'s postdoc research fellowship are funded through the ERC Starting Grant "DrugsInPregnancy" (grant no. 678033).

AUTHOR CONTRIBUTIONS

J. N. T. analyzed the data and drafted the manuscript. J. N. T., A. L., and H. N. planned the study, interpreted

the results, and revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

REFERENCES

1. Daw JR, Hanley GE, Greyson DL, *et al.* Prescription drug use during pregnancy in developed countries: a systematic review. *Pharmacoepidemiol Drug Saf* 2011; **20**: 895–902.
2. Mitchell AA, Gilboa SM, Werler MM, *et al.* Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. *Am J Obstet Gynecol* 2011; **205**: 51–58.
3. Engeland A, Bramness J, Daltveit A, *et al.* Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106 000 pregnancies in Norway 2004–2006. *Br J Clin Pharmacol* 2008; **65**: 653–660.
4. Lupattelli A, Spigset O, Twigg MJ, *et al.* Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open* 2014; **4** e004365.
5. Nordeng H. Drug utilization in pregnant women. In *Drug Utilization Research: Methods and Applications*, Elseviers M (ed.). Chichester: John Wiley & Sons Ltd, 2016; 240–247.
6. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet C Semin Med Genet* 2011; **157c**: 175–182.
7. Schaefer C, Peters P, Miller RK. *Drugs During Pregnancy and Lactation. Treatment Options and Risk Assessment*. Academic Press: London, 2015.
8. Addis A, Sharabi S, Bonati M. Risk classification systems for drug use during pregnancy: are they a reliable source of information? *Drug Saf* 2000; **23**: 245–253.
9. Doering P, Boothby LA, Cheok M. Review of pregnancy labeling of prescription drugs: is the current system adequate to inform of risks? *Am J Obstet Gynecol* 2002; **187**: 333–339.
10. Merlob P, Stahl B. Classification of drugs for teratogenic risk: an anachronistic way of counseling. *Teratology* 2002; **66**: 61–62.
11. Gagne JJ, Maio V, Berghella V, *et al.* Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy. *Eur J Clin Pharmacol* 2008; **64**: 1125–1132.
12. Olesen C, Sorensen HT, De Jong-Van Den Berg L, *et al.* Prescribing during pregnancy and lactation with reference to the Swedish classification system. A population-based study among Danish women. *Acta Obstet Gynecol Scand* 1999; **78**: 686–692.
13. Schirm E, Meijer WM, Tobi H, *et al.* Drug use by pregnant women and comparable non-pregnant women in The Netherlands with reference to the Australian classification system. *Eur J Obstet Gynecol Reprod Biol* 2004; **114**: 182–188.
14. Lacroix I, Damase-Michel C, Lapeyre-Mestre M, *et al.* Prescription of drugs during pregnancy in France. *Lancet* 2000; **356**: 1735–1736.
15. WHO Collaborating Centre for Drugs Statistics Methodology. *ATC Classification Index with DDDs*. Norwegian Institute of Public Health: Oslo, 2015.
16. Läkemedelsindustriföreningen. FASS for vårdpersonal. Available from: http://www.fass.se/LIF/startpage (accessed 1 June 2016).
17. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Lippincott Williams & Wilkins: New York, 2008.
18. Australian Government Department of Health. Australian categorisation system for prescribing medicines in pregnancy. Available from: https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy (accessed 1 June 2016).
19. U.S. Food and Drug Administration. FDA Online Label Repository. Available from: http://labels.fda.gov/ (accessed 1 June 2016).
20. Hale TW. *Medications and Mother's Milk*. Hale Publishing L.P: Amarillo, 2012.
21. Hardin JW, Hilbe JM. *Generalized Estimating Equations*. CRC Press: Boca Raton, 2013.
22. Malm H, Borisch C. Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and antigout medications. In *Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment*, Schaefer C, Peters P, Miller RK (eds.). Academic Press: London, 2015; 27–58.
23. Goldstein L, Weber-Shöndorfer C, Berkovitch M. Nausea and vomiting in pregnancy. In *Drugs During Pregnancy and Lactation. Treatment Options and Risk Assessment*, Schaefer C, Peters P, Miller RK (eds.). Academic Press: London, 2015; 75–91.
24. Riley EH, Fuentes-Afflick E, Jackson RA, *et al.* Correlates of prescription drug use during pregnancy. *J Womens Health* 2005; **14**: 401–409.
25. Yang T, Walker MC, Krewski D, *et al.* Maternal characteristics associated with pregnancy exposure to FDA category C, D, and X drugs in a Canadian population. *Pharmacoepidemiol Drug Saf* 2008; **17**: 270–277.
26. Van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? *Am J Epidemiol* 2010; **172**: 1292–1298.
27. Ekman A, Dickman PW, Klint A, *et al.* Feasibility of using web-based questionnaires in large population-based epidemiological studies. *Eur J Epidemiol* 2006; **21**: 103–111.
28. U.S. Food and Drug Administration. FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425317.htm (accessed 27 June 2016).

SUPPORTING INFORMATION

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

Paper II

Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children

II

Johanne N. Trønnes, Mollie Wood, Angela Lupattelli, Eivind Ystrom, Hedvig Nordeng

Paediatr Perinatal Epidemiol vol. 34 (2020), pp. 247-256. DOI: 10.1111/ppe.12568

Received: 21 January 2019 | Revised: 14 May 2019 | Accepted: 8 June 2019

DOI: 10.1111/ppe.12568

SPECIAL ISSUE:
ACETAMINOPHEN-NEURODEVELOPMENT

Paediatric and Perinatal Epidemiology WILEY

Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children

Johanne N. Trønnes[1] | Mollie Wood[1,2] | Angela Lupattelli[1] | Eivind Ystrom[1,3,4] | Hedvig Nordeng[1,5]

[1]PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway

[2]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

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

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

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

Correspondence
Hedvig Nordeng, Department of Pharmacy, University of Oslo, Oslo, Norway.
Email: h.m.e.nordeng@farmasi.uio.no

Funding information
This work was supported by the European Research Council Starting Grant "DrugsInPregnancy" (grant no. 639377) and the Norwegian Pharmaceutical Society (to JNT). MoBa is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract no. NO1-ES-75558), NIH/NINDS (grant nos. UO1 NS 047537-01, UO1 NS047537-06A1), and the Norwegian Research Council/FUGE (grant no. 151918/S10).

Abstract

Background: Recent studies have suggested an association between prenatal paracetamol exposure and adverse neurodevelopmental outcomes in children. However, these findings may be confounded by unmeasured factors related to maternal use of paracetamol and child outcomes.

Objective: To examine the association between duration and timing of prenatal paracetamol exposure on parent-reported communication skills, behaviour, and temperament in preschool-aged children, with focus on the role of unmeasured confounding.

Methods: We used data from the Norwegian Mother and Child Cohort Study. Linear and generalised linear models with inverse probability weights and robust standard errors were used to quantify the association between prenatal paracetamol exposure and continuous and categorical outcomes.

Results: Of the 32 934 children included in our study, 8374 (25.4%), 4961 (15.1%), and 1791 (5.4%) were prenatally exposed to paracetamol in one, two, and three trimesters, respectively. Children exposed to paracetamol in two trimesters scored lower on shyness compared with unexposed children (β −0.62, 95% confidence interval [CI] −1.05, −0.19). Children exposed to paracetamol in three trimesters had a moderate increased risk of internalising behaviour problems (relative risk (RR) 1.36, 95% CI 1.02, 1.80) and borderline externalising behaviour problems (RR 1.22, 95% CI 0.93, 1.60) compared with unexposed children. Children exposed to paracetamol in 2nd/3rd trimester scored lower on shyness (β −0.32, 95% CI −0.66, 0.02) compared with unexposed children. Sensitivity analyses indicated that unmeasured confounders play an important role and may potentially bias the effect estimates away from the null.

Conclusions: Timing of exposure and short-term use of paracetamol during pregnancy do not seem to pose any substantial risk of the outcomes examined. Although we found an association between paracetamol use in multiple trimesters and lower shyness and greater internalising behaviour in preschool-aged children, we cannot rule out chance or unmeasured confounding as possible explanations for these findings.

KEYWORDS
child neurodevelopment, MoBa, paracetamol, pregnancy

1 | BACKGROUND

Since 2013, several studies of multiple birth cohorts have suggested an association between paracetamol exposure during pregnancy and adverse neurodevelopmental outcomes in children.[1-9] Paracetamol crosses the placenta and the blood-brain barrier, and several biologically plausible mechanisms for interfering with foetal brain development have been suggested, including neurotoxicity induced by oxidative stress,[10,11] interaction with maternal hormones (thyroid and sex hormones) important for normal brain development,[12] and stimulation of endocannabinoid receptors required for normal axonal growth and fasciculation. However, prior findings may be confounded by unmeasured factors related to maternal use of paracetamol and child outcomes. Given the widespread use of paracetamol among 40%-65% of pregnant women,[13,14] establishing its long-term neurodevelopmental safety continues to be of great public health interest.

Determining the effect of prenatal paracetamol exposure on child neurodevelopment is challenging. The term "neurodevelopment" encompasses a wide range of domains,[15] and though previous studies have focused mainly on attention deficit hyperactivity disorder (ADHD) and behavioural outcomes,[9,16] other outcomes, such as communication skills and temperament, are also important domains within the realm of neurodevelopment. Moreover, bias and confounding are problems encountered with observational data.[17] In particular, unmeasured confounding poses important challenges, as we do not know the magnitude or direction of bias and cannot account for it fully.[18] To address unmeasured confounding, two recent studies used paternal paracetamol use as a negative control in relation to child outcomes, with conflicting results.[4,9] Prior to those two studies, Brandlistuen and colleagues[1] employed a sibling design, which partially accounts for familial and genetic confounding, and found that long-term paracetamol exposure was associated with adverse neurodevelopmental outcomes in 3-year-old children in the Norwegian Mother and Child Cohort Study.

It is important to examine the association between paracetamol use in pregnancy and child neurodevelopment at different child ages.[19] We build on previous research within the Norwegian Mother and Child Cohort Study (MoBa)[1,8] and reassesses child neurodevelopment at 5 years. We investigate the association between prenatal exposure to paracetamol and communication, externalising and internalising behaviour, and temperament in preschool-aged children and explore the role of unmeasured confounding.

SYNOPSIS

Study question

We investigated the association between prenatal paracetamol exposure and parent-reported communication skills, behavioural, and temperamental problems in preschool-aged children and explored the role of unmeasured confounding.

What's already known

Recent studies have suggested an association between prenatal paracetamol exposure and adverse neurodevelopmental outcomes in children. Given the widespread use of paracetamol during pregnancy, establishing its long-term neurodevelopmental safety is of great public health interest.

What this study adds

We found no substantial associations between timing of prenatal paracetamol exposure on the outcomes examined. Paracetamol use in multiple trimesters was associated with lower shyness and greater internalising behaviour in preschool-aged children. However, we cannot rule out chance or confounding by unmeasured factors as possible explanations for our findings.

2 | METHODS

2.1 | Study population and data collection

This is a sub-study of the MoBa conducted by the Norwegian Institute of Public Health. The MoBa is a population-based pregnancy cohort that recruited pregnant women in Norway between 1999 and 2008 at their routine ultrasound examination at gestational week 17-18.[20] The initial participation rate was 41%. The cohort now includes 114 500 children. Mothers completed questionnaires at regular intervals during the pregnancy (gestational ages 17, 22, and 30 weeks) and after the child was born (6 months, 18 months, 3 years, and 5 years of age). MoBa data were linked to the Medical Birth Registry of Norway (MBRN) via the woman's personal identification number. MBRN includes information on pregnancy, delivery, and neonatal health for all births in Norway.[21] The MoBa was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

This study used data from the MoBa study (Data version 9, released 2015). We included women who had completed the questionnaires with information on medication exposure in pregnancy at GWs 17 and 30 (Q1, Q3) and 6 months postpartum (Q4). Women who used combination drugs including paracetamol were excluded in order to enable us to study the impact of paracetamol in itself. Figure 1 shows an overview of dropout and exclusion criteria. The study sample with complete information at baseline included 69 555 children, of which 32 934 (47.3%) had outcome data at 5 years. A comparison of the study sample with full cohort is given in Table S1, including the amount of missingness for each covariate. A comparison of exposure rates and characteristics of the mother-child pairs with the outcome measured and those lost to follow-up are given in Table S2.

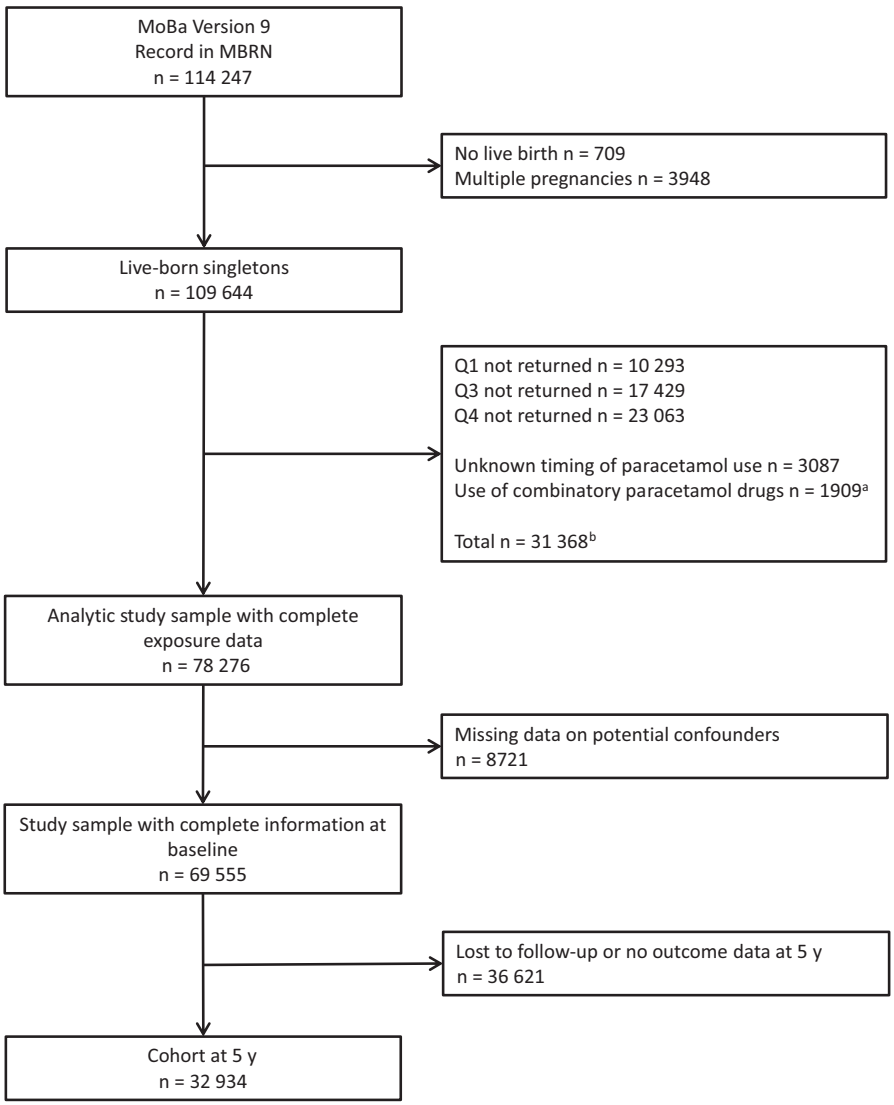


FIGURE 1 Participant flow chart. [a]Use of drugs with ATC code N02BE51 or N02AA59. [b]Conditions may overlap. Abbreviation: y, years

2.2 | Paracetamol exposure

Information about medication use was obtained from two prenatal and one postnatal questionnaire. Women were presented with a list of indications where they could report the name of the medication taken in an open textbox along with timing of use (6 months pre-pregnancy, GW 0-4, 5-8, 9-12, 13+ (Q1), 13-16, 17-20, 21-24, 25-28 and 29+ (Q3), and week 30 until delivery (Q4)) and for how many days they had used it, according to a specific indication (eg "back pain," "pelvic girdle pain," and "headache").

All medications were coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.[22] Paracetamol exposure was defined as the use of a medication with ATC code N02BE01. In Norway, paracetamol is available both over-the-counter and by prescription, and is the first-line analgesic in pregnancy. In the primary analysis, we explored the durational effects of prenatal paracetamol exposure. Duration of paracetamol use was defined according to the number of trimesters it was used: (a) paracetamol use in one trimester, (b) paracetamol use in two trimesters, (c) paracetamol use in three trimesters, and (d) no use during pregnancy (mutually exclusive groups). Within these categories, we explored the average number of days of paracetamol use. As a secondary analysis, we explored the effect of timing (first-trimester exposure (yes/no) and 2nd-3rd trimester exposure (yes/no)). Women who used paracetamol prior to pregnancy only constituted the negative control group. A table showing various patterns of paracetamol exposure can be found in the Table S3.

2.3 | Neurodevelopmental outcomes

Communication skills were assessed by the Ages and Stages Questionnaire (ASQ), which is considered to be an effective screening tool for detecting developmental delays. The communication domain consists of seven questions regarding the child's language competence,[23] and mothers answered "Yes," "A few times," or "Not yet" to statements according to whether the child could do the

TABLE 1 Maternal and child characteristics of the 5-year cohort (n = 32 934) according to paracetamol exposure during pregnancy

	No use of paracetamol during pregnancy (n = 17 808)	Paracetamol use in one trimester (n = 8374)	Paracetamol use in two trimesters (n = 4961)	Paracetamol use in three trimesters (n = 1791)
Maternal characteristics				
Mean age at time of delivery, years (SD)	30.8 (4.4)	30.4 (4.3)	30.5 (4.3)	30.8 (4.3)
Married/cohabiting, n (%)	17 215 (96.7)	8104 (96.8)	4807 (96.9)	1748 (97.6)
Primiparous, n (%)	9113 (51.2)	4072 (48.6)	2130 (42.9)	638 (35.6)
University/college education, n (%)	13 738 (77.2)	6385 (76.3)	3772 (76.0)	1348 (75.3)
Mean pre-pregnancy BMI, kg/m^2 (SD)	23.5 (3.9)	23.9 (4.1)	24.4 (4.3)	24.9 (4.7)
Folic acid supplement, n (%)	15 190 (85.3)	7216 (86.2)	4346 (87.6)	1588 (88.7)
Symptoms of anxiety/depression[a], *z* score (SD)	-0.09 (0.8)	-0.01 (0.9)	0.04 (0.9)	0.18 (1.0)
Smoking during pregnancy, n (%)				
No	14 726 (82.7)	6632 (79.2)	3931 (79.2)	1414 (79.0)
Yes	680 (3.8)	412 (4.9)	266 (5.4)	85 (4.8)
Stopped	2402 (13.5)	1330 (15.9)	764 (15.4)	292 (16.2)
Alcohol intake during pregnancy, n (%)				
No or minimal	15 789 (88.7)	7305 (87.2)	4357 (87.8)	1526 (85.2)
Low to moderate	1851 (10.4)	972 (11.6)	568 (11.5)	239 (13.3)
Frequent	168 (0.9)	97 (1.2)	36 (0.7)	26 (1.5)
Health conditions, n (%)				
Headache or migraine	3257 (18.3)	3202 (38.2)	3137 (68.2)	1399 (78.1)
Pain[b]	11 093 (62.3)	5908 (70.6)	3719 (75.0)	1451 (81.0)
Fever or infections	4244 (23.8)	3535 (42.2)	2182 (44.0)	806 (45.0)
Co-medications, n (%)				
NSAIDs (M01A, N02BA)	629 (3.5)	680 (8.1)	558 (11.3)	322 (18.0)
Opioids (N02A)	14 (0.1)	20 (0.2)	15 (0.3)	13 (0.7)
Psychotropic drugs[c]	371 (2.1)	220 (2.6)	152 (3.1)	78 (4.4)
Triptans (N02CC)	66 (0.4)	64 (0.8)	(100 (2.0)	61 (3.4)
Child characteristics				
Boy, n (%)	9198 (51.7)	4208 (50.3)	2523 (50.9)	861 (48.1)
Preterm[d] (<37 weeks), n (%)	753 (4.3)	377 (4.5)	210 (4.3)	69 (3.9)
Low birthweight[d] (<2500 g), n (%)	402 (2.3)	225 (2.7)	139 (2.8)	32 (1.8)
Malformations[d], n (%)	881 (5.0)	385 (4.6)	245 (4.9)	86 (4.8)

[a]Measured by a short version of the Hopkins Symptoms Checklist (SCL-5) in Q1 and Q3.
[b]Includes back pain, neck and shoulder pain, pelvic girdle pain, and other pains in muscle/joints.
[c]Psychotropic drugs were further divided into the following groups in the statistical analyses: antidepressants (N06A), antipsychotics (N05A), antiepileptics (N03A), stimulants (N06BA), benzodiazepines (N05BA, N05CD), and benzodiazepine-like drugs (N05CF).
[d]Not included in IPT weighting based on DAG.

activity. Mean scores were calculated and standardised for all children with a response to at least six of the seven items on the scale. Communication problems were defined as children with T scores ≥65.[24]

Selected items from The Child Behaviour Checklist (CBCL) for preschool children (CBCL/1.5-5) was used to assess children's behaviour.[25] The CBCL/1.5/5 has several subscales (attention problems, aggressive behaviour, emotionally reactive, anxious/depressed, and somatic complaints) which are combined with 2 aggregated scales measuring externalising (the first 2 subscales) and internalising behaviour (the last 3 subscales). Mothers reported the extent to which they agreed with the behaviour statements using the response categories "Not true," "Somewhat or sometimes true," or "Very true or often true." Mean scores were calculated and standardised for all children with complete outcome data. Children with T scores ≥63 were classified as having clinically significant externalising or internalising behaviour problems.[26]

Temperament was assessed by the short version of the Emotionality, Activity and Shyness Temperament Questionnaire (EAS), which measures the four temperament dimensions

emotionality, activity, sociability, and shyness.[27,28] Mothers reported how well the statements applied to their child's behaviour using a five-response Likert scale ranging from "Not at all typical" to "Very typical." As these are temperamental traits, akin to normal personality traits, there is no recommended cut-off. Higher T scores indicate children who are more emotional, more active, more sociable, or more shy.

All outcomes were parent-reported when the child was 5 years old. Additional information about items comprising the scales and Cronbach's α can be found in the supplementary material and Table S4.

2.4 | Covariates

Potential confounders and risk factors for the outcomes were identified through a literature review and directed acyclic graphs (Figure S1).[29] We included maternal age at delivery, marital status, education level, parity, pre-pregnancy body mass index (BMI), folic acid supplement, smoking habits, alcohol use, symptoms of anxiety and depression (measured by a short version of the Hopkins Symptoms Checklist (SCL-5)[30]), maternal health conditions during pregnancy, concomitant medication use, and child sex as covariates in the analysis. An overview of the sources of the covariates is provided in Table S5. Additional and more detailed information on the covariates can be found in the Supplementary Material.

2.5 | Statistical analysis

To account for measured differences between the women who used paracetamol during pregnancy and those who did not, we used propensity scores (PS) to calculate inverse probability of treatment weights (IPTW).[31] All PS models were fit using logistic regression to estimate the probability of taking paracetamol in one trimester (model 1), two trimesters (model 2), and three trimesters (model 3) versus no use, respectively, conditional on measured confounders. We also fit PS models to estimate the probability of paracetamol use in the first trimester versus no use in the first trimester (model 4), and paracetamol use in the second/third trimester, but not in the first trimester versus no use during pregnancy (model 5), both conditional on measured confounders. Stabilised IPTW were calculated based on the estimated PS and the balance assessed by standardised differences (Table S6). A standardised difference <0.1 was considered acceptable.[31] Two interaction terms were included in the third model (pain conditions by headache/migraine and depression scores by headache/migraine) to ensure sufficient balance between covariates.

To account for loss to follow-up at 5 years, we estimated stabilised inverse probability of censoring weights (IPCW), up-weighting the women who remained to represent similar women who dropped out from the baseline sample (n = 69 555).[32] These weights included the same variables as the PS models, except that the interaction terms were removed from model 3. Characteristics of the weights are presented in Table S7. We fit outcome models with combined weights (IPTW × IPCW). Generalised linear models (with a negative binomial distribution and log link) and linear models were used to evaluate categorical outcomes (ASQ and CBCL) and continuous outcomes (EAS), respectively. Robust standard errors were used to calculate 95% confidence intervals (CIs).

We carried out multiple analyses to assess unmeasured confounding. First, we estimated the association between our negative control group and neurodevelopmental outcomes.[33,34] Second, we investigated the treatment effect within different percentiles of the PS[35] and asymmetrically trimmed the range of the PS[36] for our main findings. Third, we used the bounding factor analysis to assess the impact of unmeasured confoudning.[37]

Sensitivity analyses investigating the association between prenatal paracetamol exposure and neurodevelopmental outcomes within different indications, analyses restricted to term pregnancies, a principal component analysis, and a probabilistic bias analysis can be found in the Supplementary Material. All methods are described in more detail in the Supplementary Material.

Stata MP version 14.1 was used for all statistical analyses.

3 | RESULTS

Among the 32 934 children who had outcome data at 5 years, 15 126 (45.9%) were born to mothers who had used paracetamol at least once during the pregnancy, and the most common indications for use were pain conditions, headache or migraine, and fever or infection. Overall, 8374 (25.4%), 4961 (15.1%), and 1791 (5.4%) women took paracetamol in one, two, or three trimesters, respectively. Within these categories, the average number of days reported was 3, 9, and 24, respectively. Characteristics of mother-child pairs are presented in Table 1. Women who used paracetamol during pregnancy were less likely to be first-time mothers, used co-medications more frequently, had more health problems, smoked more, and reported a low to moderate intake of alcohol more often than unexposed women.

3.1 | Neurodevelopmental outcomes

The prevalence of outcomes in the 5-year cohort was 7.5% for communication problems, 9.8% for externalising behavioural problems, and 10.3% for internalising behavioural problems. We found an increased risk of internalising (adjusted relative risk (RR) 1.36, 95% CI 1.02, 1.80) and externalising behaviour problems (RR 1.22, 95% CI 0.93, 1.60) in children whose mothers used paracetamol in three trimesters compared to unexposed children (Table 2). Children born to mothers who used paracetamol in two trimesters scored lower on shyness than unexposed children (adjusted β −0.62, 95% CI −1.05, −0.19; Table 3). We found no association between timing of paracetamol use during pregnancy and the outcomes examined (Tables 4 and 5). However, children exposed to paracetamol in 2nd/3rd trimester scored lower

TABLE 2 Associations between duration of paracetamol exposure during pregnancy and communication and behavioural problems in preschool-aged children

Communication and behavioural problems[a]	Total n	Percentage with outcome	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Communication problems				
Never user	17 317	7.4	1.00 (Reference)	1.00 (Reference)
Paracetamol use in one trimester	8180	7.4	1.00 (0.91, 1.09)	0.98 (0.88, 1.09)
Paracetamol use in two trimesters	4835	7.4	1.00 (0.89, 1.11)	0.85 (0.73, 1.00)
Paracetamol use in three trimesters	1757	8.5	1.15 (0.98, 1.35)	1.18 (0.86, 1.60)
Externalising problems				
Never user	17 283	9.4	1.00 (Reference)	1.00 (Reference)
Paracetamol use in one trimester	8136	10.1	1.08 (1.00, 1.17)	1.03 (0.95, 1.14)
Paracetamol use in two trimesters	4823	10.0	1.06 (0.97, 1.17)	1.00 (0.87, 1.14)
Paracetamol use in three trimesters	1742	12.5	1.33 (1.17, 1.52)	1.22 (0.93, 1.60)
Internalising problems				
Never user	17 446	9.8	1.00 (Reference)	1.00 (Reference)
Paracetamol use in one trimester	8213	10.7	1.09 (1.01, 1.18)	1.03 (0.95, 1.13)
Paracetamol use in two trimesters	4857	10.3	1.04 (0.95, 1.15)	0.92 (0.81, 1.05)
Paracetamol use in three trimesters	1754	12.7	1.29 (1.13, 1.47)	1.36 (1.02, 1.80)

Note: Adjusted estimates are weighted with combined weights (IPTW × IPCW).
Abbreviations: RR, relative risk; CI, confidence interval.
[a]Communication skills were assessed by the ASQ and behaviour problems by the CBCL.

on shyness than unexposed children (adjusted β −0.32, 95% CI −0.66, 0.02).

3.2 | Assessment of unmeasured confounding

In the negative control analysis, 2843 women used paracetamol prior to pregnancy only, and 14 965 women were unexposed during pregnancy. Paracetamol use before pregnancy only was associated with communication problems (RR 1.19, 95% CI 1.02, 1.38) and lower activity levels in children (β −0.80, 95% CI −1.23, −0.36) in adjusted models (Tables S8 and S9).

We observed a non-uniform treatment effect across different strata of the PS for the effect of paracetamol exposure in three trimesters on internalising behaviour and the effect of paracetamol exposure in two trimesters on shyness (Tables S10 and S11). Asymmetric trimming resulted in slightly reduced effect estimates for internalising behaviour, but not for shyness (Tables S12 and S13). A closer investigation of women exposed to paracetamol in three trimesters who also were in the low tail of the PS (n = 11) revealed that these women used paracetamol with high frequency and reported more offspring internalising problems, but did not report using paracetamol for any of the most common indications.

The bounding factor analysis showed that confounding of strength equal to an RR of 2.06 (on both sides) could completely explain away an observed RR of 1.36 between paracetamol use in three trimesters and internalising behaviour problems, but a weaker confounder could not.

Additional results are available in the Supplementary Material.

4 | COMMENT

4.1 | Principal findings

In our primary analyses, according to duration of paracetamol exposure we found a moderate increased risk of internalising behaviour and a borderline increased risk of externalising behaviour in children exposed to paracetamol in three trimesters compared with unexposed children. Children exposed to paracetamol in two trimesters scored lower on shyness than unexposed children, but the difference in mean T scores was small (50.1 vs 49.8). In secondary analyses by timing of exposure, we found a small borderline association between exposure to paracetamol in the 2nd/3rd trimester and lower shyness, which is in line with findings from the duration analysis. Even though disentangling the effect of duration from timing is challenging, the effect estimates for shyness were in the same direction, albeit the latter estimate was of smaller magnitude. Sensitivity analyses indicated that unmeasured confounding plays an important role and we cannot rule out chance or unmeasured confounding as possible explanations for our findings.

4.2 | Strengths of the study

By using data from the MoBa study, we have the unique opportunity to study the potential long-term effects of medications in pregnancy due to its large sample size, prospective design, and long follow-up.

TABLE 3 Associations between duration of paracetamol exposure during pregnancy and temperamental traits in preschool-aged children

Temperament[a]	Total n	Mean T score (SD)	Unadjusted β (95% CI)	Adjusted β (95% CI)
Emotionality				
Never user	17 416	49.7 (10.0)	0.00 (Reference)	0.00 (Reference)
Paracetamol use in one trimester	8228	50.1 (9.9)	0.31 (0.05, 0.57)	0.24 (−0.06, 0.53)
Paracetamol use in two trimesters	4858	50.2 (9.9)	0.46 (0.14, 0.77)	−0.01 (−0.44, 0.41)
Paracetamol use in three trimesters	1756	50.6 (10.1)	0.81 (0.31, 1.30)	0.13 (−1.08, 1.33)
Activity				
Never user	17 612	49.9 (10.0)	0.00 (Reference)	0.00 (Reference)
Paracetamol use in one trimester	8303	49.9 (10.0)	0.03 (−0.23, 0.29)	−0.08 (−0.38, 0.21)
Paracetamol use in two trimesters	4901	49.9 (9.9)	-0.02 (−0.33, 0.29)	−0.04 (−0.48, 0.39)
Paracetamol use in three trimesters	1771	50.1 (10.2)	0.25 (−0.25, 0.75)	0.51 (−0.57, 1.60)
Sociability				
Never user	17 604	50.0 (9.9)	0.00 (Reference)	0.00 (Reference)
Paracetamol use in one trimester	8298	50.0 (9.9)	0.06 (−0.20, 0.32)	0.02 (−0.27, 0.32)
Paracetamol use in two trimesters	4908	50.2 (10.0)	0.23 (−0.09, 0.54)	0.30 (−0.12, 0.73)
Paracetamol use in three trimesters	1777	50.1 (9.8)	0.03 (−0.45, 0.51)	−0.07 (−1.02, 0.88)
Shyness				
Never user	17 512	50.1 (10.0)	0.00 (Reference)	0.00 (Reference)
Paracetamol use in one trimester	8252	50.0 (9.9)	−0.10 (−0.36, 0.16)	−0.17 (−0.46, 0.13)
Paracetamol use in two trimesters	4874	49.8 (9.8)	−0.30 (−0.61, 0.01)	−0.62 (−1.05, −0.19)
Paracetamol use in three trimesters	1760	50.0 (10.0)	−0.07 (−0.56, 0.42)	−0.24 (−1.27, 0.80)

Note: Adjusted estimates are weighted with combined weights (IPTW × IPCW).
Abbreviations: SD, standard deviation; CI, confidence interval.
[a]Temperamental traits were assessed by the EAS.

The MoBa provides detailed information on a range of variables, including maternal sociodemographic and lifestyle factors, medication use, and indications of use. An important strength of our study was that we were able to adjust for the indication of use, which is important given that some of the indications for which paracetamol is used may have effects on foetal health.[38] Furthermore, we used advanced statistical methods to control for important confounders and performed a robust set of additional analyses to investigate the role of unmeasured confounding, as well as other sources of bias.

4.3 | Limitations of the study

The MoBa has a low participation rate with a possibility of self-selection of the healthiest women. Prior studies have shown that prevalence estimates may not be generalisable; however, the measures of tested associations were valid in MoBa.[39] Although we used IPCWs to account for loss to follow-up at 5 years, we cannot rule out that selection bias may have affected our results. Both exposure and outcomes were parent-reported and subject to misclassification. Probabilistic bias analysis revealed that non-differential exposure misclassification may have resulted in underestimating the true exposure effects. On the other hand, dependent misclassification is possible.[40] Importantly, it is likely that biases from misclassification and confounding act jointly, but in opposite directions, and our results should be interpreted with this in mind. No information on formulation or dose was available; however, we examined days of use in order to get a better understanding of exposure duration.

4.4 | Interpretation

This study is a follow-up of the MoBa and adds to the current literature on long-term neurodevelopment of children prenatally exposed to paracetamol by more closely exploring the role of unmeasured confounding. It is reassuring that the use of paracetamol in one trimester was not associated with communication, behavioural, or temperamental problems in children 5 years of age and also that timing of paracetamol use during pregnancy does not seem to increase the risk of the outcomes examined. Furthermore, paracetamol exposure during pregnancy did not seem to have a negative impact on communication skills among preschool-aged children.

Across the lifespan, shyness is associated with a variety of social and emotional problems, particularly along the internalising dimension.[41] Our association between prenatal paracetamol exposure and less shyness in children was not due to low levels of positive emotionality (ie low extraversion and low activity), but was specific to shyness. This may indicate a more undifferentiated expression of feelings among the children.[41] In novel situations, a moderate fear of strangers is normative for preschool-aged children and the effect

TABLE 4 Associations between timing of paracetamol exposure and communication and behavioural problems in preschool-aged children

Communication and behavioural problems[a]		Total n	Percentage with outcome	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Communication problems					
Paracetamol use in 1st trimester	No	23 706	7.4	1.00 (Reference)	1.00 (Reference)
	Yes	8383	7.6	1.03 (0.94, 1.12)	0.98 (0.88, 1.08)
Paracetamol use in 2nd/3rd trimester[b]	No	17 317	7.4	1.00 (Reference)	1.00 (Reference)
	Yes	6389	7.4	1.00 (0.90, 1.10)	0.97 (0.86, 1.10)
Externalising problems					
Paracetamol use in 1st trimester	No	23 632	9.7	1.00 (Reference)	1.00 (Reference)
	Yes	8352	10.3	1.06 (0.99, 1.14)	0.99 (0.91, 1.08)
Paracetamol use in 2nd/3rd trimester[b]	No	17 283	9.4	1.00 (Reference)	1.00 (Reference)
	Yes	6349	10.5	1.12 (1.02, 1.21)	1.09 (0.98, 1.20)
Internalising problems					
Paracetamol use in 1st trimester	No	23 859	10.0	1.00 (Reference)	1.00 (Reference)
	Yes	8411	11.1	1.10 (1.02, 1.19)	0.99 (0.91, 1.07)
Paracetamol use in 2nd/3rdtrimester[b]	No	17 446	9.8	1.00 (Reference)	1.00 (Reference)
	Yes	6413	10.5	1.06 (0.98, 1.16)	1.05 (0.95, 1.16)

Note: Adjusted estimates are weighted with combined weights (IPTW × IPCW).
Abbreviations: RR, relative risk; CI, confidence interval.
[a]Communication skills were assessed by the ASQ and behaviour problems by the CBCL.
[b]Paracetamol use in 2nd and/or 3rd trimester, but not in 1st trimester.

could represent dysregulated behaviour, but the clinical meaning of this finding is uncertain.

Earlier publications from the MoBa found an association between prenatal paracetamol exposure for 28 days or more, and communication problems, externalising and internalising behaviour problems, and higher activity levels in 3-year-old children.[1] Communication problems were also present at 18 months.[8] After 5 years of follow-up, only internalising behaviour problems remained. We could not replicate the association between long-term prenatal exposure to paracetamol and communication or activity problems observed in younger children. An explanation for the different findings may be that problems detected in early childhood have resolved by 5 years of age because symptoms of emotional and behavioural problems may change or evolve as a child grows older.[42] We must also keep in mind that some problems are detected more easily when the child is older; therefore, it is important to re-assess neurodevelopmental outcomes in children after a longer follow-up period.[15] When comparing our exposure definition with prior studies,[1,8] 56.4% of the women reporting use of paracetamol for more than 28 days, were classified as exposed in three trimesters in our study.

4.5 | Bias from unmeasured confounding

If there is a causal effect of paracetamol exposure during pregnancy on child neurodevelopment, we would expect a null finding in the negative control analysis as paracetamol used prior to pregnancy cannot directly impact neurodevelopment. However, we found positive associations between our negative control group[34] and some child outcomes, though different outcomes than those identified in the main analyses. This indicates that there is unmeasured confounding and our observed associations may be confounded to some extent by unobserved maternal factors, such as personality traits[43] or genetics. There could be unobserved factors related to analgesic use and adherence during pregnancy that cause the observed observations. Using a similar methodological approach, Harris et al[44] recently found an unexpected association between maternal triptan use during pregnancy and offspring sociability at 5 years. Moreover, the non-uniform treatment effect across the PS supports the presence of unmeasured confounding.[35,36] Asymmetric trimming could not fully wash away the observed associations, but the effect estimate of paracetamol use in three trimesters on internalising behaviour was reduced and further attenuated when we excluded women in the low tail of the PS (n = 11). The bounding factor analysis showed that only a strong confounder can fully explain away the observed exposure-outcome association. Given the magnitude of the association between high contentiousness and use of paracetamol during pregnancy (odds ratio 0.74 (95% CI 0.55, 0.99),[43] maternal personality traits may not fully explain our finding. However, these analyses suggest that unmeasured confounding plays an important role and may, at least in part, possibly explain our results.

In this study, we examined three important domains of neurodevelopment, namely communication skills, behaviour, and temperament by using screening instruments widely recognised within child psychiatry and psychology.[24,26,27] These tools show high internal consistency and are strongly predictive of later child diagnosis.[23,26,28] As MoBa is an ongoing study, future studies should describe trajectories of early childhood problems and their association with later diagnosis. Moreover, there is a need for international authoritative

TABLE 5 Associations between timing of paracetamol exposure and temperamental traits in preschool-aged children

Temperament[a]		Total n	Mean T score (SD)	Unadjusted β (95% CI)	Adjusted β (95% CI)
Emotionality					
Paracetamol use in 1st trimester	No	23 828	49.8 (9.9)	0.00 (Reference)	0.00 (Reference)
	Yes	8430	50.3 (10.0)	0.42 (0.18, 0.67)	0.16 (−0.12, 0.44)
Paracetamol use in 2nd/3rd trimester[b]	No	17 416	49.8 (10.0)	0.00 (Reference)	0.00 (Reference)
	Yes	6412	50.1 (9.9)	0.30 (0.02, 0.59)	0.21 (−0.12, 0.55)
Activity					
Paracetamol use in 1st trimester	No	24 085	49.9 (10.0)	0.00 (Reference)	0.00 (Reference)
	Yes	8502	49.9 (10.0)	−0.05 (−0.29, 0.20)	−0.03 (−0.32, 0.26)
Paracetamol use in 2nd/3rd trimester[b]	No	17 612	49.9 (10.0)	0.00 (Reference)	0.00 (Reference)
	Yes	6473	50.0 (10.0)	0.11 (−0.16, 0.40)	−0.02 (−0.36, 0.32)
Sociability					
Paracetamol use in 1st trimester	No	24 066	50.0 (9.9)	0.00 (Reference)	0.00 (Reference)
	Yes	8521	50.2 (9.9)	0.17 (−0.07, 0.41)	0.21 (−0.07, 0.49)
Paracetamol use in 2nd/3rd trimester[b]	No	17 604	49.9 (9.9)	0.00 (Reference)	0.00 (Reference)
	Yes	6462	50.0 (9.9)	0.02 (−0.25, 0.31)	0.00 (−0.33, 0.35)
Shyness					
Paracetamol use in 1st trimester	No	23 952	50.0 (9.9)	0.00 (Reference)	0.00 (Reference)
	Yes	8445	50.0 (10.0)	−0.05 (−0.30, 0.20)	−0.17 (−0.45, 0.11)
Paracetamol use in 2nd/3rd trimester[b]	No	17 512	50.0 (10.0)	0.00 (Reference)	0.00 (Reference)
	Yes	6441	49.9 (9.8)	−0.23 (−0.51, 0.05)	−0.32 (−0.66, 0.02)

Note: Adjusted estimates are weighted with combined weights (IPTW × IPCW).
Abbreviations: SD, standard deviation; CI, confidence interval.
[a]Temperamental traits were assessed by the EAS.
[b]Paracetamol use in 2nd and/or 3rd trimester, but not in 1st trimester.

guidance on how to measure neurodevelopmental outcomes in medication safety in pregnancy studies.[45]

5 | CONCLUSIONS

Overall, paracetamol use as short term or at different timing in pregnancy does not seem to have a negative impact on child communication, behaviour, or temperament in preschool-aged children. Children exposed to paracetamol in two trimesters scored lower on shyness, and children exposed to paracetamol in three trimesters had a moderate increased risk of internalising behaviour problems compared with unexposed children. However, some evidence suggests that unmeasured confounding could possibly explain these findings. Pregnant women should be empowered to make appropriate decisions about their use of over-the-counter analgesics such as paracetamol during pregnancy to avoid both overuse and underuse of over-the-counter analgesics and avoid unfounded concerns about the risks of paracetamol to the unborn child.

ACKNOWLEDGEMENTS

The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all of the participating families in Norway who take part in this ongoing cohort study.

ORCID

Johanne N. Trønnes https://orcid.org/0000-0001-8462-0917
Mollie Wood https://orcid.org/0000-0002-9302-2641
Angela Lupattelli https://orcid.org/0000-0002-8787-3183
Eivind Ystrom https://orcid.org/0000-0003-4390-6171
Hedvig Nordeng https://orcid.org/0000-0001-6361-2918

REFERENCES

1. 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;42:1702-1713.
2. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatrics*. 2014;168:313-320.
3. Thompson JM, Waldie KE, Wall CR, Murphy R, Mitchell EA. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PLoS ONE*. 2014;9:e108210.
4. Stergiakouli E, Thapar A, Davey SG. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. *JAMA Pediatrics*. 2016;170:964-970.

5. Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal use of acetaminophen and child IQ: a Danish cohort study. *Epidemiology*. 2016;27:912-918.
6. Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. *Int J Epidemiol*. 2016;45:2009-2017.
7. Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. *Int J Epidemiol*. 2016;45:1987-1996.
8. Vlenterie R, Wood M, Brandlistuen RE, Roeleveld N, van Gelder M, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. *Int J Epidemiol*. 2016;45:1998-2008.
9. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics*. 2017;140:e20163840.
10. Posadas I, Santos P, Blanco A, Munoz-Fernandez M, Cena V. Acetaminophen induces apoptosis in rat cortical neurons. *PLoS ONE*. 2010;5:e15360.
11. Ghanizadeh A. Acetaminophen may mediate oxidative stress and neurotoxicity in autism. *Med Hypotheses*. 2012;78:351.
12. Frye C, Bo E, Calamandrei G, et al. Endocrine disrupters: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. *J Neuroendocrinol*. 2012;24:144-159.
13. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol*. 2005;193:771-777.
14. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open*. 2014;4:e004365.
15. Bromley RL, Baker GA. Fetal antiepileptic drug exposure and cognitive outcomes. *Seizure*. 2017;44:225-231.
16. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav*. 2018;101:125-147.
17. Wood M, Lapane KL, van Gelder M, Rai D, Nordeng H. Making fair comparisons in pregnancy medication safety studies: an overview of advanced methods for confounding control. *Pharmacoepidemiol Drug Saf*. 2018;27:140-147.
18. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol*. 2007;166:646-655.
19. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev*. 2003;27:3-18.
20. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2016;45:382-388.
21. Irgens LM. The Medical Birth Registry of Norway; a source for epidemiological and clinical research. *Scand J Rheumatol Suppl*. 1998;107:105-108.
22. WHO Collaborating Centre for Drugs Statistics Methodology. ATC/DDD index 2016. https://www.whocc.no/atc_ddd_index/. Accessed September 20, 2016.
23. Richter J, Janson H. A validation study of the Norwegian version of the ages and stages questionnaires. *Acta Paediatr*. 2007;96:748-752.
24. Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: ages and stages questionnaires. *J Pediatr Psychol*. 1997;22:313-328.
25. Novik TS. Validity of the child behaviour checklist in a Norwegian sample. *Eur Child Adolesc Psychiatry*. 1999;8:247-254.
26. Achenbach TM, Ruffle TM. The child behavior checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev*. 2000;21:265-271.
27. Buss AH, Plomin R. *Temperament: Early Developing Personality Traits*. Hillsdale, NJ: Lawrence Erlbaum Associates Inc; 1984.
28. 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.
29. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10:37-48.
30. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry*. 2003;57:113-118.
31. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res*. 2011;46:399-424.
32. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168:656-664.
33. Lipsitch M, Tchetgen ET, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21:383-388.
34. Weisskopf MG, Tchetgen Tchetgen EJ, Raz R. Commentary: On the use of imperfect negative control exposures in epidemiologic studies. *Epidemiology*. 2016;27:365-367.
35. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol*. 2006;163:262-270.
36. Stürmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution-a simulation study. *Am J Epidemiol*. 2010;172:843-854.
37. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology*. 2016;27:368-377.
38. Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. *Pediatrics*. 2014;133:e674-688.
39. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23:597-608.
40. Kristensen P. Bias from nondifferential but dependent misclassification of exposure and outcome. *Epidemiology*. 1992;3:210-215.
41. Karevold E, Ystrom E, Coplan RJ, Sanson AV, Mathiesen KS. A prospective longitudinal study of shyness from infancy to adolescence: stability, age-related changes, and prediction of socio-emotional functioning. *J Abnorm Child Psychol*. 2012;40:1167-1177.
42. de Fays L, Van Malderen K, De Smet K, et al. Use of paracetamol during pregnancy and child neurological development. *Dev Med Child Neurol*. 2015;57:718-724.
43. Ystrom E, Vollrath ME, Nordeng H. Effects of personality on use of medications, alcohol, and cigarettes during pregnancy. *Eur J Clin Pharmacol*. 2012;68:845-851.
44. Harris GE, Wood M, Ystrom E, Nordeng H. Prenatal triptan exposure and neurodevelopmental outcomes in 5-year-old children: Follow-up from the Norwegian Mother and Child Cohort Study. *Paediatr Perinat Epidemiol*. 2018;32:247-255.
45. Nordeng H, Lupattelli A, Wood M. Prenatal exposure to antidepressants and increased risk of psychiatric disorders. *BMJ*. 2017;358:j3950.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. *Paediatr Perinat Epidemiol*. 2020;34:247–256. https://doi.org/10.1111/ppe.12568

Paper III

Association of timing and duration of prenatal analgesic opioid exposure with attention-deficit/hyperactivity disorder in children

Johanne N. Trønnes, Angela Lupattelli, Marte Handal, Svetlana Skurtveit, Eivind Ystrom, Hedvig Nordeng

JAMA Netw Open, vol. 4, no. 9 (2021), pp. e2124324. DOI: 10.1001/jamanetworkopen.2021.24324

III

JAMA Network Open

Original Investigation | Pediatrics

Association of Timing and Duration of Prenatal Analgesic Opioid Exposure With Attention-Deficit/Hyperactivity Disorder in Children

Johanne Naper Trønnes, MScPharm; Angela Lupattelli, PhD; Marte Handal, MD, PhD; Svetlana Skurtveit, PhD; Eivind Ystrom, PhD; Hedvig Nordeng, PhD

Abstract

IMPORTANCE Prior studies have reported that the use of illicit opioids during pregnancy is associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) in offspring; however, evidence regarding the association of analgesic opioids is limited.

OBJECTIVE To examine the association of timing and duration of prenatal analgesic opioid exposure with ADHD in children.

DESIGN, SETTING, AND PARTICIPANTS This cohort study uses data from the Norwegian Mother, Father and Child Cohort study (1999-2008), a nationwide birth cohort study linked to national health registries, with a mean (SD) follow-up of 10.8 (2.2) years. A total of 73 784 live-born singleton children born to 62 013 mothers who reported a pain-related condition before and/or during pregnancy were included, with 2 comparator groups: (1) mothers who did not use any opioids and (2) mothers who used opioids before pregnancy only. Data were analyzed from June to December 2020.

EXPOSURES Maternal self-report of analgesic opioid use during pregnancy, by timing (early and middle and/or late) and duration (≥5 weeks vs ≤4 weeks).

MAIN OUTCOMES AND MEASURES Diagnosis of ADHD or filled prescription for ADHD medication in children and symptoms of ADHD at child age 5 years, measured by Conners' Parent Rating Scale–Revised. Inverse probability of treatment weights were used to control for measured confounding. Cox regression was used to estimate hazard ratios (HRs) and 95% CIs.

RESULTS The analyses of ADHD diagnosis and ADHD symptoms included 73 480 children (35 996 [49.0%] girls; mean [SD] maternal age, 30.0 [4.6] years) and 31 270 children (15 377 [49.2%] girls; mean [SD] maternal age, 30.5 [4.4] years), respectively. Overall, 1726 children in the ADHD diagnosis sample (2.3%) and 667 children in the ADHD symptom sample (2.1%) were exposed to an analgesic opioid at least once during gestation. No associations between timing of prenatal analgesic opioid exposure and ADHD diagnosis or symptoms was found. Exposure for 5 or more weeks was associated with an increased risk of ADHD diagnosis (HR, 1.60, 95% CI, 1.04-2.47) compared with exposure for 4 weeks or less; however, there was no such association for the risk of ADHD symptoms.

CONCLUSIONS AND RELEVANCE In this cohort study, a slightly elevated risk of ADHD diagnosis after prenatal analgesic opioid exposure for 5 or more weeks was found compared with exposure for 4 weeks or less. This result may be driven by longer duration of use; however, the role of residual or unmeasured confounding cannot be excluded. This finding needs to be replicated in other studies.

JAMA Network Open. 2021;4(9):e2124324. doi:10.1001/jamanetworkopen.2021.24324

Key Points

Question Is prenatal analgesic opioid exposure associated with attention-deficit/hyperactivity disorder (ADHD) in children?

Findings In this cohort study of 73 480 children, with a mean follow-up of 11 years, no association between timing of analgesic opioid exposure during pregnancy and ADHD was found. The risk of ADHD diagnosis was elevated after exposure to opioids for 5 or more weeks compared with exposure for 4 weeks or less.

Meaning The increased risk of ADHD observed in this study may be driven by longer duration of exposure; however, the role of residual or unmeasured confounding cannot be excluded, and this finding requires further study.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Many women experience pain during pregnancy, and although not recommended as the first choice for pain management in pregnancy, opioids are at times prescribed due to their analgesic effect.[1,2] In recent years, consumption of prescribed opioid analgesics has increased,[3] a trend also affecting women of childbearing age.[4-7] Prevalence estimates among pregnant women range from 1% in multinational surveys[8] based on maternal self-report to 3% in Norway[9,10] and 14% to 28% in the United States based on dispensed prescriptions.[5-7]

Results from animal studies suggest that prenatal opioid exposure may alter fetal brain structure and functioning, thus potentially interfering with normal brain development.[11-13] However, evidence regarding the long-term consequences of prenatal opioid exposure on child neurodevelopment, including behavioral outcomes, is still limited.[14-16]

One of the most common behavioral disorders in childhood is attention-deficit/hyperactivity disorder (ADHD), which affects approximately 2% to 7% of children worldwide.[17,18] The median age of first diagnosis is estimated to be around 7 to 9 years.[19] The cause of ADHD is multifactorial, and ADHD has been associated with a broad range of negative outcomes later in life.[18]

Associations of prenatal opioid exposure with ADHD have been observed; however, prior studies have mainly been done in selected populations, such as women receiving opioid maintenance treatment or among women with opioid dependence.[20,21] Azuine et al[22] reported an odds ratio of 2.55 (95% CI, 1.42-4.57) for ADHD after opioid exposure when children with exposure were compared with those without. Currently, there is a knowledge gap regarding the association of prenatal analgesic opioid exposure with ADHD. This study sought to fill this gap by focusing specifically on women using analgesic opioids for pain management. The aim of this study was to examine the association between timing and duration of prenatal analgesic opioid exposure and (1) ADHD diagnosis and/or filled prescription for ADHD medications and (2) ADHD symptoms at child age 5 years.

Methods

Study Population and Data Collection

This study used data from the Norwegian Mother, Father and Child Cohort study (MoBa) (data version 9), the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), and the Norwegian Patient Registry (NPR), linked via the woman's personal identification number and pregnancy sequence (eFigure 1 in the Supplement). The establishment and data collection in MoBa was previously based on a license from the Norwegian Data protection agency and approval from The Regional Committee for Medical Research Ethics (reference No. 2015/442), and it is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical Research Ethics Written informed consent was obtained from all participants. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed.

MoBa is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health.[23] Pregnant women from all over Norway were recruited between 1999 and 2008 through a postal invitation in connection with their routine ultrasonography examination in gestational week (GW) 17 or 18. The initial participation rate was 41%, and the cohort now includes 114 500 children, 95 200 mothers, and 75 200 fathers. Mothers were followed up by paper-based questionnaires during pregnancy (in GW 17 [Q1] and 30 [Q3]) and after the child was born (at 6 months [Q4], 18 months, 3 years, 5 years [Q–5 years], 7 years, 8 years, 13 years, 14 years, and 16 to 17 years).

MBRN includes information on pregnancy, delivery, and neonatal health for all births from GW 12 in Norway.[24] The NorPD contains information about all prescribed medications (irrespective of reimbursement) to individuals in ambulatory care since 2004.[25] The NPR contains records on

admission to hospitals and specialist health care on an individual level since 2008.[26] The data include date of admission and discharge as well as primary and secondary diagnosis and cover all government-owned hospitals and outpatient clinics and all private health clinics that receive governmental reimbursement. Diagnostic codes in the NPR follow the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*).

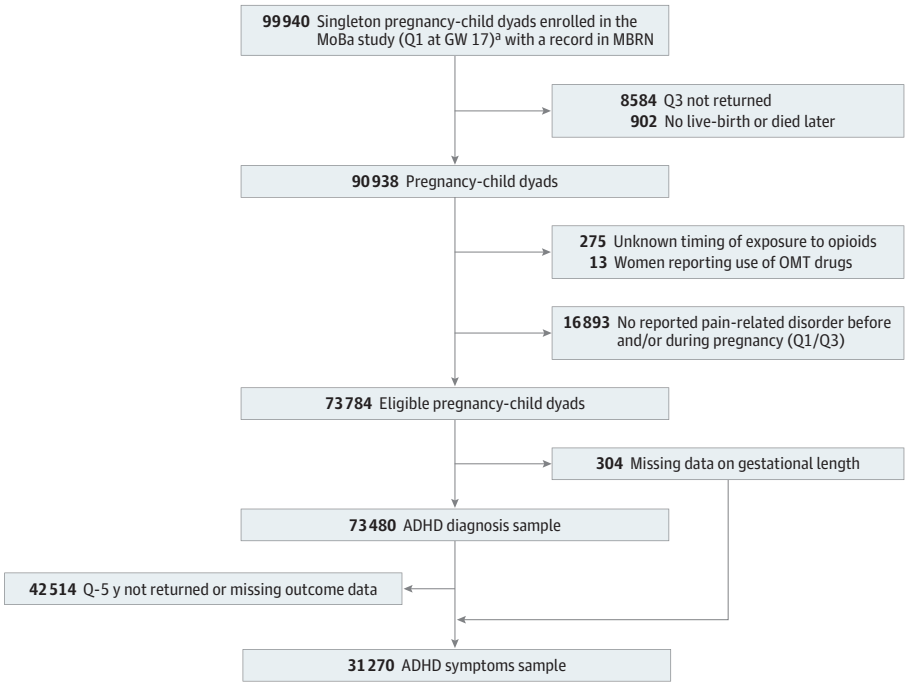
We included live-born singletons with a record in MBRN, born to women who completed the 2 prenatal questionnaires (ie, Q1 and Q3) in MoBa. Women with unknown timing of analgesic opioid exposure as well as women who reported a drug used for opioid maintenance treatment were excluded. We restricted the population to women reporting an underlying indication for treatment with analgesic opioids, ie, pain conditions, to emulate the design of a hypothetical clinical trial.[27] The list of included pain conditions is found in eTable 1 in the Supplement. **Figure 1** outlines the inclusion/exclusion criteria to achieve the final study population(s).

Analgesic Opioid Exposure

Information about medication use was obtained from MoBa Q1, Q3, and Q4. Women reported the name of the medication taken along with timing of use (6 months prepregnancy and during pregnancy by 4-week intervals [eg, GW 0-4, GW 5-8, or GW 9-12]) according to listed indications. All medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[28] The exposed group included children of women who reported use of analgesic opioids in pregnancy, defined as reporting of ATC code N02A. Individual substances included in the exposure definition appear in eTable 2 in the Supplement.

First, we examined the association of ever use of analgesic opioids in pregnancy and ADHD. Then, we examined the association of timing and duration of analgesic opioid exposure. Timing was categorized as early pregnancy (first trimester) and middle and/or late pregnancy (second and/or third trimester), while duration of exposure was defined according to whether a single interval (use in ≤4 weeks) or multiple 4-week intervals (use in ≥5 weeks) were indicated on the questionnaires.

Figure 1. Flowchart to Achieve the Final Study Population



ADHD, attention-deficit/hyperactivity disorder; MBRN, Medical Birth Registry of Norway; OMT, drugs used in opioid maintenance therapy (ie, ATC N07BC); Q, questionnaire.

[a] Q1 was the first Norwegian Mother, Father and Child Cohort Study (MoBa) questionnaire completed at gestational week (GW) 17; its completion implies enrollment into the study. Conditions of exclusion can overlap.

Among women with pain ailments before and/or during pregnancy, we defined 2 comparison groups; first, a broad group consisting of children of women who did not report use of analgesic opioids (ie, unexposed group) and, second, a narrower comparison group consisting of children of women who used analgesic opioids prior to pregnancy only (prepregnancy users only). The second comparator group was included to minimize residual confounding, given that these children have mothers whose confounder distribution may be more similar to the mothers of children exposed to opioids during pregnancy.

Outcomes

The primary outcome was child ADHD diagnosis, defined as at least 1 diagnosis of ADHD recorded in the NPR (*ICD-10* code, F90) from 2008 to 2015 and/or at least 1 filled prescription for an ADHD medication (ie, methylphenidate, atomoxetine, racemic amphetamine, dexamphetamine, and lisdexamphetamine) in NorPD between 2004 and 2016. The *ICD-10* code F90 (hyperkinetic disorder) requires the combination of both inattentive and hyperactive symptoms. The drugs listed are licensed in Norway and used for treatment of ADHD. Diagnosis and treatment are started in the specialist health care service, and 80% of children with an ADHD diagnosis receive pharmacotherapy. There is no lower age limit for receiving a F90 diagnosis; however, it is rare in children younger than 5 years.[17,29,30] Most children in MoBa were born in 2004 or later, and children born from 1999 to 2003 have available outcome data from age 4 years at the latest (eFigure 1 in the Supplement).

To identify children with difficulties but who did not meet the diagnostic criteria for ADHD, we used a secondary outcome of parent-reported symptoms of ADHD in children at age 5 years. This was measured by 12 items from the Conners' Parent Rating Scale–Revised Short Form (CPRS-R) included in the MoBa questionnaire at Q-5 years. Thus, the sample was further restricted to those with available outcome data at 5 years. Mean scores were calculated and standardized. Higher *z* scores indicated more symptoms of ADHD. More information is provided in the eMethods in the Supplement.

Potential Confounding Factors

A large number of factors may be associated with opioid use during pregnancy as well as ADHD, and these were examined with the aid of a directed acyclic graph (eFigure 2 in the Supplement).[31-33] We included the following covariates in our analyses: maternal age, marital status, maternal education, maternal income, parity, prepregnancy body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), folic acid supplement, smoking habits, alcohol use, illicit drug use, maternal chronic conditions in early pregnancy, symptoms of anxiety and depression (measured by a short version of the Hopkins Symptoms Checklist[34] in Q1), number of pain episodes and comedications during pregnancy, and familial risk of ADHD (addressed by information about maternal and paternal filled prescriptions for ADHD medication). Additional factors (eg, child and paternal characteristics, maternal ADHD traits [Adult ADHD Self-report Scale]) were considered under alternative model specifications (eTable 3 in the Supplement). More details on covariates are given in the eMethods in the Supplement.

Statistical Analysis

To account for measured confounders, we used propensity score (PS)–based methods with inverse probability of treatment weights (IPTW).[35] The PS was estimated by a logistic regression model. First, we estimated the probability of ever exposure to analgesic opioids during pregnancy, relative to no exposure, given the previously mentioned confounders. In the analysis by timing of exposure, we estimated the probability of analgesic opioid exposure in early and middle and/or late pregnancy, relative to no exposure in the time window or among those who used opioids before pregnancy only, conditional on the previously mentioned confounders. In analysis by duration of exposure, we estimated the probability of exposure for 5 or more weeks relative to exposure for 4 or fewer weeks,

conditional on the previously mentioned confounders. Then, we derived stabilized IPTWs for all comparisons. We could not fairly compare those with opioid exposure for 5 or more weeks with those with no exposure or prepregnancy use due to a large imbalance in covariates. The balance of the covariates was assessed by standardized mean differences, with 0.15 as cutoff for evidence of imbalance.[36,37] When we were not able to achieve a standardized mean difference less than 0.15 between covariates in weighted populations, the covariates were added to the final weighted model. Characteristics of the weights are presented in eTable 4 in the Supplement. The PS and subsequent weights were estimated in each imputed data set to obtain exposure effect estimates in each imputation and then combined to produce an overall estimate.[38,39]

To estimate the hazard ratio (HR) for ADHD, we performed crude and weighted Cox regression analysis with robust standard errors. We used child age in years as the time scale and a quadratic term for year of birth. The follow-up period started at birth and ended on the date of ADHD diagnosis, date of first drug prescription for ADHD, or December 31, 2016, whichever came first. To estimate standardized mean differences in ADHD symptoms, we fit crude and weighted generalized linear models with robust standard errors. Statistical significance was set at $P < .05$, and all tests were 2-tailed. All statistical analysis were performed using Stata MP version 16.1 (StataCorp). Data were analyzed from June to December 2020.

Sensitivity Analyses

We performed several subgroup and sensitivity analyses. First, we conducted separate models for all exposure definitions that considered additional parental and child factors under alternate model specifications (eTable 3 in the Supplement). Second, we performed stratified analysis by child sex, with ever or never exposure to analgesic opioids in pregnancy to better understand the association of child sex with ADHD risk. Third, we performed a positive control analysis among women using opioid cough medications (ATC, R05D) during pregnancy. A commonly used opioid in Norway is the combinatory product of codeine and paracetamol, and we performed an analysis among women using opioids not in combination with paracetamol. To evaluate unmeasured confounding, we calculated the E value, ie, the minimum strength of an unmeasured confounder would need to have with both the exposure and the outcome to account for the association.[40] In a subsample of women with data available in both MoBa and NorPD (2004-2009), we crosschecked maternal self-reported opioid use with NorPD data and looked at the average defined daily dose (DDD) dispensed to describe the amount of opioids. More information and additional sensitivity analyses are presented in the eMethods in the Supplement.

Missing Data and Multiple Imputation

Pattern of missingness was explored, and nearly 20% of the pregnancies had missing values in at least 1 of the sufficient confounders. Under the assumption that data were missing at random, we imputed incomplete data via multiple imputation with chained equation (10 replications).[41,42] Information on missing values on covariates and the imputation procedure is provided in the eMethods in the Supplement.

Results

We had 73 480 children of 61 753 mothers with data on ADHD diagnosis (ADHD diagnosis sample; 35 996 [49.0%] girls; mean [SD] maternal age, 30.0 [4.6] years) and 31 270 children of 26 017 mothers with data on ADHD symptoms (ADHD symptoms sample; 15 377 [49.2%] girls; mean [SD] maternal age, 30.5 [4.4] years) (Figure 1). Most children in the ADHD symptoms sample were also included in the ADHD diagnosis sample. Of these children, 1726 in ADHD diagnosis sample (2.3%) and 667 in ADHD symptoms sample (2.1%) were exposed to an analgesic opioid at least once during gestation. The dominating substance was codeine in combination with paracetamol, reported in approximately 90% of the exposed pregnancies. The other substances reported were mainly strong

opioids (eTable 2 in the Supplement). The main pain conditions reported among analgesic opioid users were headache or migraine (751 of 1726 [43.5%]), back pain (741 [43.0%]), and pelvic girdle pain (401 [23.2%]). Most women had a college or university education, but mothers of children with exposure were more likely to report smoking, alcohol, and use of comedications during pregnancy. Further characteristics are presented in **Table 1** and eTable 5 in the Supplement.

ADHD Diagnosis

In total, 2211 children (3.0%) had ADHD, and **Figure 2** shows its cumulative hazard. Fewer than 5 children were diagnosed before the age of 3 years. The incidence rate was highest at age 7 to 11 years (eTable 6 in the Supplement), and the mean (SD) follow-up time was 10.8 (2.2) years. In crude analysis, ever exposure to analgesic opioids during pregnancy was associated with a higher risk of ADHD (HR, 1.71; 95% CI, 1.38-2.10) compared with no exposure. After weighting, the association was attenuated and no longer statistically significant (weighted HR, 1.32; 95% CI, 0.98-1.76). Exposure in early and middle and/or late pregnancy was associated with a moderate increased risk of ADHD in crude analysis when compared with no exposure in the same time window (**Table 2**). However, on weighting, the point estimates were attenuated, and the confidence intervals included the null (early exposure: weighted HR, 1.34; 95% CI, 0.90-2.02; middle and/or late exposure: weighted HR, 1.32; 95% CI, 0.92-1.89). No associations were found in analyses comparing analgesic opioid use in early or middle and/or late pregnancy to prepregnancy use only (early exposure: weighted HR, 1.13; 95% CI: 0.71-1.79; middle and/or late exposure: weighted HR, 1.08; 95% CI, 0.70-1.68). Exposure for 5 weeks or more of pregnancy was associated with increased risk of ADHD (weighted HR, 1.60; 95% CI, 1.04-2.47) compared with exposure for 4 or fewer weeks (**Table 3**).

ADHD Symptoms

We found no associations between ever exposure to analgesic opioids during pregnancy and symptoms of ADHD at child age 5 years (weighted β = 0.03; 95% CI, −0.07 to 0.12) compared with no exposure. No associations were found in analyses of timing or duration (≥5 weeks vs ≤4 weeks: weighted β = −0.05; 95% CI: −0.25 to 0.15) (Table 2 and Table 3).

Sensitivity Analyses

The point estimates under alternative model specifications were generally consistent with main findings (eFigures 3, 4, and 5 in the Supplement). In analyses stratified by sex, the weighted HRs among boys and girls were similar (boys: HR, 1.28; 95% CI, 0.93-1.77; girls: HR, 1.36; 95% CI, 0.74-2.51). Furthermore, we found no association between sex and ADHD symptoms in children aged 5 years (eMethods in the Supplement).

We found no associations between children exposed to opioid-containing cough medications during pregnancy and ADHD diagnosis (weighted HR, 0.70; 95% CI, 0.47 to 1.05) or symptoms (weighted β = 0.01; 95% CI, −0.10 to 0.12) compared with no exposure. We found no associations between children exposed to analgesic opioids not in combination with paracetamol and ADHD diagnosis (weighted HR, 0.59; 95% CI, 0.23 to 1.53) or ADHD symptoms (weighted β = 0.12; 95% CI, −0.21 to 0.45) compared with no exposure during pregnancy (eMethods in the Supplement). In a subsample of participants with data available in both MoBa and NorPD (50 925 mother-child pairs), the mean (SD) DDDs dispensed among women using opioids for 4 or fewer weeks and 5 or more weeks were 8.6 (8.5) DDD and 37.2 (79.0) DDD, respectively. Results of additional sensitivity analyses are presented in the eMethods in the Supplement (eTables 7, 8, and 9, and eFigure 6, and 7 in the Supplement).

Discussion

We found no associations between timing of analgesic opioid exposure during pregnancy and ADHD, both as diagnosis and symptoms. The risk of ADHD was slightly increased after exposure for 5 or

Table 1. Characteristics of 73 480 Pregnancies in the ADHD Diagnosis Sample According to Exposure Status

Characteristic	Individuals in ADHD diagnosis sample by opioid exposure, No. (%)		
	No exposure (n = 70 916)	Exposure (n = 1726)	Prepregnancy exposure only (n = 838)
Maternal characteristics			
Age at time of delivery, mean (SD), y	30.0 (4.5)	30.4 (4.6)	29.6 (4.8)
Married or cohabiting	68 169 (96.1)	1636 (94.8)	795 (94.9)
Primiparous	31 972 (45.1)	694 (40.2)	463 (55.3)
Education			
University or college education	47 108 (66.4)	1050 (60.8)	495 (59.1)
Missing	311 (0.4)	5 (0.3)	3 (0.4)
Gross yearly income[a]			
Average	48 424 (68.3)	1137 (65.9)	569 (67.9)
Low	12 536 (17.7)	369 (21.4)	176 (21.0)
High	7585 (10.7)	163 (9.4)	75 (9.0)
Missing	2371 (3.3)	57 (3.3)	18 (2.2)
Prepregnancy BMI, mean (SD)	24.1 (4.3)	25.1 (4.9)	24.8 (4.7)
Missing, No. (%)	1761 (2.4)	21 (2.4)	41 (2.5)
Folic acid supplement	54 630 (77.0)	1275 (73.9)	671 (80.1)
Smoking[b]			
No	53 927 (76.0)	1163 (67.4)	555 (66.2)
Yes	5797 (8.2)	232 (13.4)	121 (14.4)
Stopped	10 343 (14.6)	313 (18.1)	157 (18.7)
Missing	849 (1.2)	18 (1.1)	5 (0.7)
Alcohol intake[b]			
No or minimal	61 464 (86.7)	1441 (83.5)	727 (86.8)
Low to moderate	1671 (2.4)	55 (3.2)	21 (2.5)
Frequent	58 (0.1)	3 (0.2)	0
Missing	7723 (10.9)	227 (13.2)	90 (10.7)
Symptoms of anxiety/depression, mean score (SD)[c]	1.3 (0.4)	1.4 (0.5)	1.4 (0.5)
Missing, No. (%)	2473 (3.4)	72 (4.1)	28 (3.3)
Chronic health conditions[d]	8841 (12.5)	330 (19.1)	166 (19.8)
Comedications during pregnancy[e]	37 986 (53.6)	1476 (85.5)	541 (64.6)
Illicit drug use[b]	135 (0.2)	11 (0.6)	9 (1.1)
ADHD prescriptions[f]	768 (1.1)	48 (2.8)	21 (2.5)
Child characteristics			
Boys	36 185 (51.0)	879 (50.9)	420 (50.1)
Girls	34 731 (49.0)	847 (49.1)	418 (49.9)
Preterm (<37 weeks)	3060 (4.3)	109 (6.3)	44 (5.3)
Low birth weight (<2500 g)	1713 (2.4)	57 (3.3)	18 (2.2)
All malformations	3317 (4.7)	81 (4.7)	37 (4.4)
Paternal characteristics			
Age, y			
<25	3492 (4.9)	76 (4.4)	58 (6.9)
25-29	16 571 (23.4)	396 (22.9)	217 (25.9)
30-34	27 459 (38.7)	655 (37.9)	288 (34.4)
≥35	23 216 (32.7)	593 (34.4)	273 (32.6)
Missing	178 (0.3)	6 (0.4)	2 (0.2)

(continued)

Table 1. Characteristics of 73 480 Pregnancies in the ADHD Diagnosis Sample According to Exposure Status (continued)

Characteristic	Individuals in ADHD diagnosis sample by opioid exposure, No. (%)		
	No exposure (n = 70 916)	Exposure (n = 1726)	Prepregnancy exposure only (n = 838)
Education			
University or college education	35 697 (50.3)	769 (44.6)	368 (43.9)
Missing	746 (1.1)	14 (0.8)	14 (1.7)
ADHD prescriptions (%)[f]	536 (0.8)	28 (1.6)	7 (0.8)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Gross yearly income was classified as follows: average, $17 450 to $46 540; low, less than $17 450; high, ≥$46 541.

[b] Measured in the first Norwegian Mother, Father and Child Cohort study questionnaire.

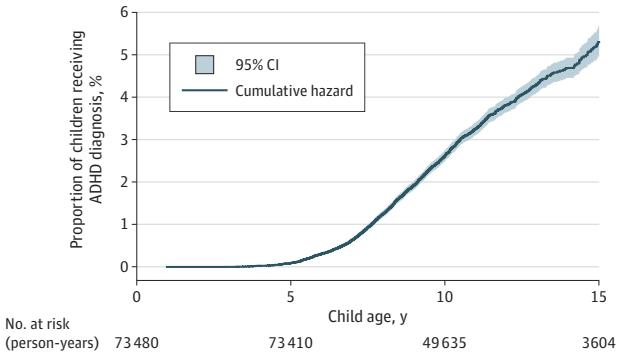
[c] Measured by a short version of the Hopkins Symptoms Checklist on first questionnaire.

[d] Chronic health conditions include the following conditions: asthma, diabetes, hypertension, Crohn disease, arthritis, lupus, epilepsy, multiple sclerosis, and cancer.

[e] Comedications in pregnancy include paracetamol, triptans, anti-epileptics, antipsychotics, antidepressants, nonsteroidal anti-inflammatory drugs, and benzodiazepines and benzodiazepine-like drugs.

[f] Indicates filled prescriptions for ADHD medication ever in life since 2004.

Figure 2. Nelson-Aalen Cumulative Hazard Estimate and the Estimated Proportion of Children Receiving a Diagnosis for Attention-Deficit/Hyperactivity (ADHD) by Child Age



more weeks compared with exposure for 4 or fewer weeks. However, there was no evidence for such an association in relation to ADHD symptoms in children at age 5 years. Our results may indicate that the increased risk of ADHD could be driven by longer duration of use; however, the role of residual confounding cannot be ruled out.

All women included in the study reported having an underlying indication for treatment with analgesic opioids, ie, pain conditions; however, there is a heterogeneity of pain-related disorders. Therefore, we included a second comparator group consisting of women who used analgesic opioids prior to pregnancy only. The group with prepregnancy opioid use only may be a fairer comparison group, with a more similar confounder structure as women using opioid analgesics in pregnancy because both groups have a history of analgesic opioid exposure. Consequently, residual confounding by indication for use is reduced. In light of this, our results provide some evidence that there is most likely no causal link between the timing of prenatal analgesic opioid exposure and ADHD, both as symptoms and diagnosis.

The most reported substance among opioid exposed women was the combined product of codeine and paracetamol, and our results are most representative for this substance. Therefore, disentangling the sole association of opioids may be challenging. We tried to address this by excluding women using the combined product in a sensitivity analysis, and we found no associations

with ADHD or symptoms among children with vs without exposure. Prior studies[43,44] have reported a positive association between paracetamol use during pregnancy and ADHD in children, showing HRs of a magnitude of 1.37 (95% CI, 1.19-1.59) for receiving a diagnosis of hyperkinetic disorder following ever exposure in pregnancy and an HR of 2.20 (95% CI, 1.50-3.24) for ADHD diagnosis following exposure to paracetamol for more than 29 days during pregnancy. Whether this association is causal or due to bias is a debated topic.[45,46] The combined product of paracetamol and codeine may be used under circumstances that are more heterogeneous than stronger opioids, and our latter finding may indicate that confounding might play a larger role on our findings.

Longer duration of use may be indicative of a more severe pain condition. We tried to address this by including number of reported pain episodes in our models as a proxy of pain severity. We acknowledge the lack of data of how severe this pain was, and we cannot rule out unmeasured confounding by pain severity.

ADHD and its symptoms are highly heritable,[18,47] and we tried to address this by including information about proxies of parental ADHD (maternal and paternal filled prescriptions for ADHD medications) in all models and maternal ADHD traits in a subsample. This did not substantially

Table 2. Association Between Timing of Prenatal Analgesic Opioid Exposure and ADHD Diagnosis and ADHD Symptoms in Children Aged 5 Years

Exposure window	No.	Events, No.	IR per 1000 person-years	Crude HR (95% CI)	Weighted HR (95% CI)
ADHD diagnosis sample					
Exposure vs no exposure					
No opioids in early pregnancy	72 675	2166	2.8	1 [Reference]	1 [Reference]
Opioids in early pregnancy	805	45	5.0	1.76 (1.30 to 2.36)	1.34 (0.90 to 2.02)
No opioids in middle or late pregnancy	72 244	2145	2.8	1 [Reference]	1 [Reference]
Opioids in middle and/or late pregnancy	1236	66	4.9	1.76 (1.38 to 2.25)	1.32 (0.92 to 1.89)
Exposure vs prepregnancy exposure only					
Opioid use in prepregnancy only	838	39	4.2	1 [Reference]	1 [Reference]
Opioids in early pregnancy	805	45	5.0	1.17 (0.76 to 1.80)	1.13 (0.71 to 1.79)
Opioids in middle and/or late pregnancy	1236	66	4.9	1.16 (0.78 to 1.72)	1.08 (0.70 to 1.68)
ADHD symptoms sample					
Exposure window	**No.**	**Mean**	**SD**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Exposure vs no exposure					
No opioids in early pregnancy	30 973	1.38	0.39	[Reference]	[Reference]
Opioids in early pregnancy	297	1.41	0.42	0.09 (−0.03 to 0.22)	0.08 (−0.08 to 0.24)
No opioids in middle or late pregnancy	30 779	1.38	0.39	[Reference]	[Reference]
Opioids in middle and/or late pregnancy	491	1.40	0.38	0.05 (−0.04 to 0.14)	−0.02 (−0.13 to 0.08)
Exposure vs prepregnancy exposure only					
Opioids prepregnancy only	334	1.43	0.40	[Reference]	[Reference]
Opioids in early pregnancy	297	1.41	0.42	−0.04 (−0.20 to 0.13)	0.05 (−0.14 to 0.24)
Opioids in middle and/or late pregnancy	491	1.40	0.38	−0.08 (−0.22 to 0.07)	−0.02 (−0.19 to 0.16)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; IR, incidence rate.

Table 3. Association Between Duration of Prenatal Analgesic Opioid Exposure and ADHD Diagnosis and ADHD Symptoms in Children Aged 5 Years

Length of exposure	No.	Events, No.	IR per 1000 person-years	Crude HR (95% CI)	Weighted HR (95% CI)
ADHD diagnosis sample					
Exposed in ≤4 weeks	1084	48	4.0	1 [Reference]	1 [Reference]
Exposed ≥5 weeks	642	43	6.2	1.60 (1.06 to 2.41)	1.60 (1.04 to 2.47)
ADHD symptoms sample					
Length of exposure	**No.**	**Mean**	**SD**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Exposed in ≤4 weeks	423	1.41	0.40	[Reference]	[Reference]
Exposed ≥5 weeks	244	1.40	0.40	−0.01 (−0.18 to 0.15)	−0.05 (−0.25 to 0.15)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; IR, incidence rate.

change our main estimates; however, we cannot exclude the role of unmeasured genetic factors in this study.[48]

To evaluate unmeasured confounding, we found that an E value of 2.58 was required to explain our association in the duration analysis. Leppert et al[48] discuss several early-life exposures (eg, smoking, nutritional supplements, stressful life events, toxin exposure, infections, and more) associated with neurodevelopmental risk alleles. None of these factors was of an order of magnitude that could account for our observed association. However, we cannot exclude a possible role of residual or unmeasured confounding on our results.

If the association between prenatal analgesic opioid exposure and ADHD were causal, we would have expected a higher proportion of children displaying ADHD symptoms at age 5 years and a positive association in our positive control analysis of opioid-containing cough medications. However, we cannot rule out that loss of follow-up in the MoBa study have affected our findings on ADHD symptoms. Future studies on the long-term safety of analgesic opioids should include measures of dose and pain severity and include more domains of neurodevelopment, including cognition.

Limitations

This study has limitations. The MoBa study has a moderate participation rate (41%), with a possibility of self-selection of the healthiest women into the cohort.[23] Although association measures have been shown to be valid in MoBa in relation to immediate birth outcomes,[49,50] we cannot rule the impact of selection bias on our results regarding ADHD symptoms when children were aged 5 years. Furthermore, the ADHD symptoms were parent reported,[51] and although outcome misclassification cannot be ruled out, this was probably nondifferential. Also, the internal consistency of the CPRS-R is high (Cronbach α = 0.9). Due to low sample size, it was not possible to study the associations of individual opioids. We were not able to identify whether a clear duration association was in place due to low power, which prevented us from looking at more granular duration groups. Another limitation is that we did not have information regarding dosage or duration of use of opioids in MoBa. A mother who had reported use of opioids during one 4-week interval may have used the drug only once or possibly every day. However, mothers who reported use during 2 or more 4-week periods (ie, ≥5 weeks) are more likely to have consumed a higher total dose. This assumption is supported by results from the DDD analysis that showed that mothers who reported opioids in 4 or fewer weeks were dispensed an average of 8.6 DDD, and mothers who reported use in 5 or more weeks were dispensed on average 37.2 DDD. However, any conclusions with regard to duration should be interpreted with caution, as this is representative for only a subsample and not all prescribed medications are actually taken.[52]

Conclusions

In this cohort study, we found no associations between the timing of analgesic opioid exposure during pregnancy and ADHD, both as diagnosis and symptoms. The risk of ADHD was slightly increased after exposure for 5 or more weeks compared with exposure for 4 or fewer weeks. This result may be associated with longer duration of use, but we cannot exclude the potential role of residual or unmeasured confounding. This finding needs to be replicated in other studies. Adequate pain management in pregnancy should be discussed on an individual patient level, bearing in mind the benefits and risks of different analgesic therapies.

ARTICLE INFORMATION

Accepted for Publication: July 7, 2021.

Published: September 15, 2021. doi:10.1001/jamanetworkopen.2021.24324

Corresponding Author: Johanne Naper Trønnes, MScPharm, PO Box 1068, Blindern, 0316 Oslo, Norway (j.n.tronnes@farmasi.uio.no).

Author Affiliations: PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway (Trønnes, Lupattelli, Ystrom, Nordeng); Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway (Handal, Skurtveit, Ystrom); PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway (Ystrom); Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway (Nordeng).

Author Contributions: Ms Trønnes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Trønnes, Lupattelli, Handal, Skurtveit, Nordeng.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Trønnes.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Trønnes, Lupattelli.

Administrative, technical, or material support: Handal.

Supervision: Lupattelli, Ystrom, Nordeng.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the European Research Council Starting Grant DrugsInPregnancy (grant No. 639377 to Dr Nordeng). Dr Ystrom was supported by the Research Council of Norway (grant Nos. 262177 and 288083).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The Norwegian Mother, Father, and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this ongoing cohort study.

REFERENCES

1. The Norwegian Medical Association. Guidelines for pain management. Accessed November 26, 2018. https://www.legeforeningen.no/om-oss/publikasjoner/retningslinjer/retningslinjer-for-smertelindring-2009/

2. Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130. doi:10.1016/j.jpain.2008.10.008

3. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. 2015;135(5):842-850. doi:10.1542/peds.2014-3299

4. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol*. 2014;123(5):997-1002. doi:10.1097/AOG.0000000000000208

5. Epstein RA, Bobo WV, Martin PR, et al. Increasing pregnancy-related use of prescribed opioid analgesics. *Ann Epidemiol*. 2013;23(8):498-503. doi:10.1016/j.annepidem.2013.05.017

6. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology*. 2014;120(5):1216-1224. doi:10.1097/ALN.0000000000000172

7. Yazdy MM, Desai RJ, Brogly SB. Prescription opioids in pregnancy and birth outcomes: a review of the literature. *J Pediatr Genet*. 2015;4(2):56-70. doi:10.1055/s-0035-1556740

8. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open*. 2014;4(2):e004365. doi:10.1136/bmjopen-2013-004365

9. Engeland A, Bjørge T, Klungsøyr K, Hjellvik V, Skurtveit S, Furu K. Trends in prescription drug use during pregnancy and postpartum in Norway, 2005 to 2015. *Pharmacoepidemiol Drug Saf*. 2018;27(9):995-1004. doi:10.1002/pds.4577

10. Handal M, Engeland A, Rønning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *Eur J Clin Pharmacol*. 2011;67(9):953-960. doi:10.1007/s00228-011-1030-7

11. Caritis SN, Panigrahy A. Opioids affect the fetal brain: reframing the detoxification debate. *Am J Obstet Gynecol*. 2019;221(6):602-608. doi:10.1016/j.ajog.2019.07.022

12. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nat Rev Neurosci*. 2009;10(4):303-312. doi:10.1038/nrn2598

13. Ross EJ, Graham DL, Money KM, Stanwood GD. Developmental consequences of fetal exposure to drugs: what we know and what we still must learn. *Neuropsychopharmacology*. 2015;40(1):61-87. doi:10.1038/npp.2014.147

14. Walhovd KB, Moe V, Slinning K, et al. Effects of prenatal opiate exposure on brain development—a call for attention. *Nat Rev Neurosci*. 2009;10(5):390. doi:10.1038/nrn2598-c1

15. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry*. 2014; 14:104. doi:10.1186/1471-244X-14-104

16. Konijnenberg C, Melinder A. Prenatal exposure to methadone and buprenorphine: a review of the potential effects on cognitive development. *Child Neuropsychol*. 2011;17(5):495-519. doi:10.1080/09297049.2011.553591

17. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. 2007;164(6):942-948. doi:10.1176/ajp.2007.164.6.942

18. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1:15020. doi:10.1038/nrdp.2015.20

19. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustün TB. Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry*. 2007;20(4):359-364. doi:10.1097/YCO.0b013e32816ebc8c

20. Sundelin Wahlsten V, Sarman I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatr*. 2013;102(5): 544-549. doi:10.1111/apa.12210

21. Yolton K, Cornelius M, Ornoy A, McGough J, Makris S, Schantz S. Exposure to neurotoxicants and the development of attention deficit hyperactivity disorder and its related behaviors in childhood. *Neurotoxicol Teratol*. 2014;44:30-45. doi:10.1016/j.ntt.2014.05.003

22. Azuine RE, Ji Y, Chang HY, et al. Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-income, multiethnic US population. *JAMA Netw Open*. 2019;2(6): e196405. doi:10.1001/jamanetworkopen.2019.6405

23. Magnus P, Birke C, Vejrup K, et al. Cohort profile update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2016;45(2):382-388. doi:10.1093/ije/dyw029

24. Irgens LM. The Medical Birth Registry of Norway: a source for epidemiological and clinical research. *Scand J Rheumatol Suppl*. 1998;107:105-108. doi:10.1080/03009742.1998.11720780

25. Norwegian Institute of Public Health. Norwegian Prescription Database (NorPD). Accessed November 10, 2020. https://www.fhi.no/en/hn/health-registries/norpd/

26. Bakken IJ, Surén P, Håberg SE, Cappelen I, Stoltenberg C. The Norwegian Patient Register—an important source for research. Article in Norwegian. *Tidsskr Nor Laegeforen*. 2014;134(1):12-13. doi:10.4045/tidsskr.13.1417

27. Toh S, Manson JE. An analytic framework for aligning observational and randomized trial data: application to postmenopausal hormone therapy and coronary heart disease. *Stat Biosci*. 2013;5(2). doi:10.1007/s12561-012-9073-6

28. WHO Collaborating Centre for Drugs Statistics Methodology. ATC/DDD index 2021. Accessed November 10, 2020. https://www.whocc.no/atc_ddd_index/

29. Ørstavik R, Gustavson K, Rohrer-Baumgartner N, et al. *ADHD in Norway*. Norwegian Institute of Public Health; 2016.

30. Tarver J, Daley D, Sayal K. Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts. *Child Care Health Dev*. 2014;40(6):762-774. doi:10.1111/cch.12139

31. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22 (5):745. doi:10.1097/EDE.0b013e318225c2be

32. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48. doi:10.1097/00001648-199901000-00008

33. Bandoli G, Palmsten K, Flores KF, Chambers CD. Constructing causal diagrams for common perinatal outcomes: benefits, limitations and motivating examples with maternal antidepressant use in pregnancy. *Paediatr Perinat Epidemiol*. 2016;30(5):521-528. doi:10.1111/ppe.12302

34. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry*. 2003;57(2):113-118. doi:10.1080/08039480310000932

35. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. doi:10.1002/sim.6607

36. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399-424. doi:10.1080/00273171.2011.568786

37. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. *Psychol Methods*. 2010;15(3):234-249. doi:10.1037/a0019623

38. Mitra R, Reiter JP. A comparison of two methods of estimating propensity scores after multiple imputation. *Stat Methods Med Res*. 2016;25(1):188-204. doi:10.1177/0962280212445945

39. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med*. 2019;38(26):5120-5132. doi:10.1002/sim.8355

40. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

41. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393

42. Lupattelli A, Wood ME, Nordeng H. Analyzing missing data in perinatal pharmacoepidemiology research: methodological considerations to limit the risk of bias. *Clin Ther*. 2019;41(12):2477-2487. doi:10.1016/j.clinthera.2019.11.003

43. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr*. 2014;168(4):313-320. doi:10.1001/jamapediatrics.2013.4914

44. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics*. 2017;140(5):e20163840. doi:10.1542/peds.2016-3840

45. Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: a causal association or bias? *Paediatr Perinat Epidemiol*. 2020;34(3):309-317. doi:10.1111/ppe.12615

46. Wood ME. Associations between prenatal acetaminophen exposure and child neurodevelopment: truth, bias, or a bit of both? *Paediatr Perinat Epidemiol*. 2020;34(3):233-236. doi:10.1111/ppe.12658

47. Eilertsen EM, Gjerde LC, Kendler KS, et al. Development of ADHD symptoms in preschool children: genetic and environmental contributions. *Dev Psychopathol*. 2019;31(4):1299-1305.

48. Leppert B, Havdahl A, Riglin L, et al. Association of maternal neurodevelopmental risk alleles with early-life exposures. *JAMA Psychiatry*. 2019;76(8):834-842. doi:10.1001/jamapsychiatry.2019.0774

49. 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

50. Biele G, Gustavson K, Czajkowski NO, et al. Bias from self selection and loss to follow-up in prospective cohort studies. *Eur J Epidemiol*. 2019;34(10):927-938. doi:10.1007/s10654-019-00550-1

51. Kumar G, Steer RA. Factorial validity of the Conners' Parent Rating Scale-revised: short form with psychiatric outpatients. *J Pers Assess*. 2003;80(3):252-259. doi:10.1207/S15327752JPA8003_04

52. Skurtveit S, Selmer R, Odsbu I, Handal M. Self-reported data on medicine use in the Norwegian Mother and Child Cohort study compared to data from the Norwegian Prescription Database. *Norsk Epidemiol*. 2014;24(1-2):209-216. doi:10.5324/nje.v24i1-2.1824

SUPPLEMENT.

eMethods. Supplemental Methods
eTable 1. Included Pain Conditions Relevant for Opioid Use in MoBa
eTable 2. Use of Specific Opioids During Pregnancy
eTable 3. Specification of Various Treatment Models
eTable 4. Characteristics of Generated Weights By Exposure in Main Analysis
eTable 5. Characteristics of Pregnancies in the ADHD Symptoms Sample According to Exposure Status

Paper IV

Prenatal exposure to opioid analgesics and scholastic skills in fifth grade – a follow up study in the Norwegian Mother, Father, and Child Cohort Study

Johanne N. Trønnes, Angela Lupattelli, Eivind Ystrom, Hedvig Nordeng

Submitted for publication

IV

Prenatal exposure to opioid analgesics and scholastic skills in fifth grade – a follow-up study in the Norwegian Mother, Father, and Child Cohort

Johanne Naper Trønnes, MSc. Pharm,[a] Angela Lupattelli, PhD,[a] Eivind Ystrom PhD,[abc] Hedvig Nordeng, PhD,[ad]

Affiliations:

[a]PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway;

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

[c]PROMENTA Research Center, Department of Psychology, University of Oslo.

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

Corresponding author: Johanne Naper Trønnes, MSc. Pharm. Address: PO box 1068, Blindern, 0316 Oslo, Norway**.** E-mail: j.n.tronnes@farmasi.uio.no Telephone: +47-22855571

Word count: 3076

Key points

Question: What is the association between prenatal exposure to opioid analgesics and fifth-grade scholastic skills?

Findings: In this cohort study, among 64 256 children, 1483 were exposed to opioid analgesics *in utero*. Children of mothers exposed in the first trimester or exposed in two or three 4-week intervals during pregnancy had lower scores on literacy and numeracy tests, compared to children of mothers that were only exposed before pregnancy. However, associations were small in magnitude and may not be clinically relevant.

Meaning: We found that prenatal exposure to opioid analgesics did not significantly impact the fifth-grade scholastic skills of children.

Abstract

Importance: Few studies have examined the neurodevelopmental consequences of prenatal exposure to opioid analgesics. Therefore, it is crucial to gain the knowledge necessary to inform clinical decisions for pregnant women with moderate to severe pain.

Objective: To investigate the association between prenatal exposure to opioid analgesics and fifth-grade scholastic skills

Design: Cohort study based on data from the Norwegian Mother, Father, and Child Cohort (1999-2008). These data were linked to the Medical Birth Registry of Norway, and data from Statistics Norway.

Setting: Nation-wide birth cohort study in Norway

Participants: 64 256 live-born singletons, born to 54 568 mothers that reported pain during pregnancy.

Exposure: Self-reported exposure to opioid analgesics during pregnancy, characterized in terms of any exposure, the exposure timing, and the exposure duration.

Main outcome(s) and measure(s): Scores from three national tests for children in fifth grade. The tests measured scholastic skills in literacy, numeracy, and English language. Test scores were standardized to z-scores. Differences in z-scores were compared between children of mothers exposed to opioid analgesics during pregnancy and children of mothers with only pre-pregnancy opioid exposure.

Results: Of the 64 256 children included, 32 521 (50.6%) were boys, and 1483 children (2.3%) were exposed to an opioid analgesic at least once during gestation. All test scores were similar

between children with any exposure to opioid analgesics in-utero and children with only pre-pregnancy exposure. Children exposed in the first trimester and those exposed in two or three 4-week intervals during pregnancy scored lower than children of mothers with only pre-pregnancy exposures on tests in literacy (weighted β [wβ]: −0.13, 95% CI: −0.25, −0.01 and wβ: −0.19, 95% CI: −0.35, −0.04) and numeracy (wβ: −0.14, 95% CI: −0.25, −0.04 and wβ: −0.19, 95% CI: −0.34, −0.05). Associations were small in magnitude, and may not be clinically relevant.

Conclusions and relevance: In this large birth cohort, we found that prenatal exposure to opioid analgesics had no substantial negative impact on fifth grade scholastic skills. These findings are reassuring; however, adequate pain management in pregnancy should be discussed on an individual patient level, bearing in mind the benefits and risks of different analgesic therapies.

Introduction

Prescription opioid analgesics are used by 3-22% of pregnant women.[1-4] Animal research has shown that prenatal exposure to opioids alters brain structures and functions; thus, opioids might interfere with fetal neurodevelopment.[5-7] In light of the ongoing opioid epidemic[8], a major concern has been the lack of knowledge about the neurodevelopmental consequences of prenatal exposure to opioid analgesics.

To our knowledge, only four previous studies have examined the association between prenatal exposure to opioid analgesics and child neurodevelopment.[9-11] Three of those studies[11-13] were based on a large Norwegian birth cohort. Skovlund et al.[12,13] reported that prenatal analgesic opioid exposure was not associated with impaired language competence or communication skills in preschool children. However, prenatal exposures for 5 or more weeks slightly increased the risk of an attention deficit hyperactivity disorder diagnosis, compared to shorter exposures (hazard ratio [HR]: 1.60, 95% confidence interval [95% CI]: 1.04-2.47).[11] Similarly, Wen et al.[10] reported that prenatal exposures for >14 days or exposures to high cumulative opioid doses increased the risk of neurodevelopmental disorders (HR range: 1.22-1.70), compared to no exposure.

Scholastic skills are important indicators of cognitive function, but they are infrequently assessed in perinatal pharmacoepidemiologic studies.[14-16] Scholastic skills, including reading and mathematics abilities, depend on cognitive processes related to executive function and working memory.[17] Thus, scholastic skills can predict future academic achievement, career aptitudes, and socioeconomic status.[18,19]

We aimed to investigate the association between fifth-grade scholastic skills and prenatal exposure to opioid analgesics, based on any exposure, exposure timing, and exposure durations, with adjustments for important confounders.

Methods

Data sources and study sample

Data for this study were retrieved from the Norwegian Mother, Father, and Child Cohort Study (MoBa), the Medical Birth Registry of Norway (MBRN), and Statistics Norway (SSB). Data were linked via the unique personal identification number given to all residents of Norway. MoBa was a population-based pregnancy cohort study, conducted by the Norwegian Institute of Public Health.[20] Participants were recruited from all over Norway, between 1999 and 2008. In 41% of the pregnancies, women consented to cohort participation. The cohort includes 114 500 children, 95 200 mothers, and 75 200 fathers. Mothers were followed-up with paper-based questionnaires during pregnancy and after delivery. The present study is based on version 12 of the quality-assured data files released for research in 2019. The establishment of MoBa and the initial data collection was based on a license from the Norwegian Data Protection Agency and approved by The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently based on regulations related to the Norwegian Health Registry Act. The present study was approved by The Regional Committees for Medical and Health Research Ethics (reference number 2017/2205). Written informed consent was obtained from all participants.

105 The MBRN is a national health registry that has stored information on all births in Norway,
106 starting in 1967.[21] The SSB contains information from public registries.[22] For the present study,
107 we acquired data on parental education, family income, and children's school test results.
108 We included all mother-child dyads of singleton pregnancies that were enrolled in the MoBa
109 study between 2002 and 2008 and were recorded in the MBRN. In an attempt to account for
110 confounding by indication, we restricted the study sample to women that reported indications for
111 opioid analgesia during pregnancy (i.e., pain conditions; specified in eMaterial, eTable 1). Other
112 inclusion and exclusion criteria are presented in Figure 1.

113 **Exposure**

114 Medication use was self-reported by the mothers in two prenatal and one post-partum
115 questionnaire. The mothers also indicated whether they had experienced any illnesses, among a
116 long list of short- and long-term illnesses. In addition, they reported any medication use and
117 specified the timing, starting at 6 months prior to pregnancy and continuing throughout the
118 pregnancy, based on 4-week intervals (e.g., gestational weeks 0-4, 5-8, or 9-12).

119 Exposure was defined as the mother's use of analgesic opioids (N02A in the World Health
120 Organization's Anatomical Therapeutic Chemical Classification System[23]). We defined "any"
121 exposure to opioid analgesics during pregnancy as use initiated during pregnancy and also use
122 that had started before pregnancy, and continued during pregnancy. We also defined opioid
123 exposures based on timing and duration. Timing was categorized into trimesters (first trimester
124 [0-12 weeks of gestation], second trimester [13-28 weeks], and 3rd trimester [29 weeks to
125 delivery]). The duration of opioid use was indicated as the number of 4-week intervals that
126 opioids were taken during pregnancy (categorized as one, two to three, or four or more 4-week

intervals). However, use in an interval did not necessarily mean consecutive use during that period.

To evaluate the effects of opioid exposure, among all pregnant women with pain ailments, we defined two mutually exclusive reference groups. Our main reference group comprised children of mothers that used opioid analgesics only before pregnancy (pre-pregnancy exposure). In a sub-analysis, we used a reference group that comprised children of mothers that did not report opioid analgesics use before or during pregnancy (unexposed).

Outcome

The outcomes were the scores from three national standardized tests on literacy, numeracy, and English language. These tests were mandatory for fifth graders (ages 10-11 years); only children with special educational or special language training needs were exempted from a test.[24] We had access to test results for the complete population of fifth graders in the period. The test scores were standardized as z-scores, over the total population of test takers in each subject and for each test year. A z-score of −1 indicated a test score of one standard deviation (SD) lower than the population mean. More information is provided in the eMaterial, and the distribution of raw test scores is shown in eFigure 1. Raw test scores were compared between the MoBa participants and the total population of test takers (eTables 2 and 3).

Covariates

Potential confounders and risk factors for the outcome were identified, *a priori*, based on subject knowledge and directed acyclic graphs (eFigure 2).[25,26] The sources of different covariates are shown in eTable 4. The following covariates were included in our main analysis and characterized as described in Table 1: maternal age at delivery, marital status, parity, maternal

149 and paternal education levels, family income-to-needs ratio (1 year prior to childbirth), pre-
150 pregnancy body mass index, chronic maternal diseases, smoking habits before pregnancy,
151 alcohol use, use of co-medications, symptoms of anxiety and depression [27] (measured on the first
152 MoBa questionnaire), time of year the baby was born (before/after summer), and paternal age.

153 **Statistical Analysis**

154 To account for the measured confounders and risk factors, we implemented propensity score
155 (PS)[28] methods with an inverse probability of treatment weights (IPTW). Each PS was derived
156 with a logistic regression model.[29] In analyzing timing, the PS was estimated as the probability
157 of opioid analgesic exposure in the (*i*) 1st trimester, (*ii*) 2nd trimester, and (*iii*) 3rd trimester,
158 compared to only pre-pregnancy exposure. In analyzing duration, the PS was estimated as the
159 probability of opioid analgesic exposure in (*i*) one interval, (*ii*) two to three intervals, and (iii)
160 four or more intervals, compared to only pre-pregnancy exposure. Then, we derived the
161 respective weights. The covariates were balanced, based on the standardized mean differences,
162 and a standardized mean difference >0.15 indicated an imbalance (eTable 5).[30] We fit
163 generalized linear models with robust standard errors to obtain crude and weighted standardized
164 mean differences in test scores with 95% confidence intervals (95% CIs). All statistical analyses
165 were performed with STATA MP version 16.

166 **Missing data**

167 Up to 29.3% of the included pregnancies had missing values for at least one of the important
168 confounders. The variables with the highest proportion of missing values were: smoking status
169 (16.4%), alcohol use (9.4%), and depressive and anxiety symptoms (3.4%). Assumption that data
170 were missing at random, we imputed incomplete data by performing multiple imputations with

chained equations (30 replications).[31-33] Data were imputed separately for the different tests (literacy, numeracy, and English). The PS and subsequent weights were estimated in each imputed dataset. Then, the PSs were applied to estimate individual exposure effects on literacy, numeracy, and English. Finally, the individual exposure estimates were combined to produce an overall exposure estimate.[34,35]

Sub-analyses and sensitivity analyses

First, we conducted an analysis with unexposed children as the reference group. Second, we performed sex-stratified analyses to investigate whether associations between opioid exposure and scholastic skills were similar among boys and girls. Third, we conducted a complete case analysis and compared the results to the imputed dataset results. Fourth, we performed an analysis where we compared those exposed for one 4-week interval to those exposed for two or more 4-week intervals during pregnancy. Fifth, we repeated our main analysis with an alternative model specification (eTable 6). Additional sensitivity analyses are described in the eMaterial.

Results

The study included 64 256 children of 54 568 mothers (mean [SD] maternal age, 30.5 [4.5] years). Of these children, 32 521 (50.6%) were boys. Opioid analgesic use was reported in 2.3% of pregnancies (n=1483). The dominating substance was codeine combined with paracetamol, reported by 90.5% of users. Most women reported short-term use (n=937/1483 = 63.2%); i.e., opioids were used in one 4-week interval during pregnancy. Mothers of exposed children were slightly older, more likely to have previous children, and more likely to report alcohol and co-medication use, compared to mothers with pre-pregnancy analgesic opioid exposure (Table 1).

Scholastic skills

Figure 1 shows the number of children that participated in each test; the majority (96.2%) participated in all three tests. Approximately 13% of children scored one SD below the population mean on the tests. Children with any opioid analgesic exposure during pregnancy did not score lower on tests in literacy, numeracy, or English, compared to children of mothers with only pre-pregnancy opioid exposure (Table 2).

In the analyses of exposure timing, children exposed to opioid analgesics in first trimester scored lower on tests in literacy (weighted β (wβ): −0.13, 95% CI: −0.25, -0.01) and numeracy (wβ: −0.14, 95% CI: −0.25, −0.04) compared to children of mothers with only pre-pregnancy exposure. Children exposed in the second or third trimester did not score significantly worse in any subject, although they showed trends of lower scores, compared to children of mothers with only pre-pregnancy exposure.

In the analyses of duration, children exposed in two to three 4-week intervals during pregnancy scored lower on tests in literacy (wβ: −0.19, 95% CI: −0.35, −0.04) and numeracy (wβ: −0.19, 95% CI: −0.34, −0.05), compared to children of mothers with only pre-pregnancy exposure. No other exposure durations were associated with test scores in literacy, numeracy, or English.

Sensitivity analyses

In crude analyses with unexposed children as the reference group, we observed similar patterns of associations to those observed in the main analyses. However, associations were attenuated after adjustments, and all confidence intervals included the null (Table 3). In analyses stratified by sex, we found no difference between boys and girls; the point estimates were of similar magnitude and confidence intervals were overlapping (eTable 7). Results from the complete case

analyses did not differ substantially from the results from the main analysis. However, in the complete case sample, we did not observe an association between the duration of exposure and low literacy scores (data not shown). Results from the remaining sensitivity analyses are described in the eMaterial (eTable 8).

Discussion

This study was the first to examine scholastic skills in children prenatally exposed to opioid analgesics. Our findings extended our understanding of the safety of prenatal opioid analgesic exposure, in terms of neurodevelopment. In a large birth cohort, we found that children with any exposure to opioid analgesics during pregnancy showed scholastic scores similar to those of children of mothers with only pre-pregnancy exposure. However, exposure to opioid analgesics in the first trimester or during two to three 4-week intervals during pregnancy was associated with lower scores in literacy and numeracy, compared to only pre-pregnancy exposure. However, the differences in mean test scores were small, and thus, they should be interpreted with caution.

The timing and duration of medications given during pregnancy are important in assessing safety.[36] Organogenesis occurs in the first trimester, and the brain develops throughout the entire pregnancy.[37,38] A potential explanation for our observation that exposure in the first trimester was associated with lower scholastic performance might be explained by immediate birth outcomes or specific malformations, which have been associated with a high risk of cognitive impairments.[39,40] However, the literature is inconclusive regarding analgesic opioid use during pregnancy and the risk of malformations and/or immediate birth outcomes.[41-46] Therefore, the observed association might not be attributable to the risk of adverse birth outcomes.

Two recent studies[10,11] suggested that longer prenatal opioid analgesic exposures were associated with adverse neurodevelopmental outcomes. In the present study, we found that prenatal opioid analgesic exposures in two to three 4-week intervals were associated with low literacy and numeracy scores (wβ: −0.19, 95% CI: −0.35, −0 04). However, exposure in four intervals or more did not significantly affect the scores; albeit, the exposed sample size was small; thus, results should be interpreted with caution. In our sensitivity analysis, when exposures in two or more intervals were compared to exposures in one interval only, we found no difference in scholastic performance. This finding suggested that residual confounding or chance might have affected our primary analysis of exposure durations.

In the weighted sub-analysis, with unexposed children as the reference, prenatal exposures to opioid analgesics in any trimester or for any duration were not associated with lower scores on tests in literacy, numeracy, or English. Moreover, in the main analysis, when we used only pre-pregnancy exposure as reference, we found greater differences in mean scores. This finding was somewhat counterintuitive, because we expected greater differences when unexposed children comprised the reference group. However, this finding might be explained by the different weighting methods applied in the two analyses (IPTW and SMR), which may answer different questions (see eMaterials).[47]

The clinical relevance of our observations was difficult to evaluate, due to the lack of cut-off values for defining clinically significant differences. However, the observed associations were small in magnitude.[48,49] A standardized mean difference of -0.13 on literacy scores would correspond to an OR of 1.3.[50] Moreover, on all tests, the mean test scores among the exposed children were above the population mean, which indicated that their performance was not worse than that of the general population of fifth graders. Taken together, our results suggested that

prenatal exposure to opioid analgesics did not negatively impact fifth-grade scholastic skills. These findings are reassuring for pregnant women that need opioid analgesics for pain management. However, opioid analgesics are not the recommended first choice for treating pain during pregnancy. Although they may be used sporadically in the first and second trimesters[51,52], use should be avoided in the third trimester, due to an increased risk of neonatal withdrawal symptoms.[53,54]

In Norway, national tests were introduced in 2007 as part of the national quality assessment system. Because they were not based on grades or teacher evaluations, the national tests were intended to provide an objective measure of scholastic skills to identify children that performed below the level of their peers.[24] Scholastic skills reflect aspects of cognitive function[17], although the test results are not strongly correlated with IQ; instead, test results are a product of the child's concentration, knowledge, and motivation for the given test.[15,19] We decided to use the fifth-grade tests, because some disabilities are not detected until a child has problems in a school setting.[55] It is essential to identify and help children with difficulties and to put necessary measures in place, because problems with reading and writing are associated with a wide range of mental health problems, including anxiety, depression, and behavioral problems.[56]

We lack studies that examine neurodevelopmental outcomes in children after prenatal exposure to opioid analgesics.[9] Most previous studies were conducted with women that used opioids for opioid maintenance therapy or for illicit purposes.[57,58] However, those results are not generalizable to women that use opioid analgesics for pain management, due to differences in sociodemographic characteristics and lifestyle factors.[59,60] Moreover, neurodevelopment includes a wide range of domains.[55] Thus, further studies are needed to examine other outcomes that reflect the neurodevelopmental safety of analgesic opioid exposure *in utero*.[9]

Strengths and limitations

This study had several strengths, including the large sample size and information on a wide range of important confounders. We included only women with an indication for opioid analgesic use, and our reference group comprised children born to mothers with only pre-pregnancy exposure, to reduce confounding by indication. We accounted for missing data with multiple imputations. We examined associations with both the timing and duration of opioid use. Finally, the outcome was not based on teacher evaluations or grades, which limited teacher bias.

This study also had some limitations. First, scholastic skills were measured at one time point and we only evaluated children in fifth grade. We could not analyze the development of skills over time; therefore, it would be interesting to investigate performance in children at older ages. Moreover, we did not have information on opioid doses or durations in the MoBa cohort; thus, we used the number of 4-week intervals as a proxy for duration. The MoBa participation rate was 41%; thus, our cohort had a potential self-selection bias of the healthiest women.[61,62] This bias might have affected the generalizability of our findings, because parental education and socioeconomic position are important known predictors of child scholastic achievement.[63,64] We could not study the effects of individual opioids or compare strong and weak opioids, due to the low number of exposed individuals. Future studies should endeavor to distinguish between strong and weak opioids, because they may be used for different indications.[65] Furthermore, a small proportion of children (<5%) were exempted from the tests.[24] Because exemption was only granted for children in special education or special language training, we could not rule out that exemptions may have led to underestimations in the associations. Finally, we could not rule out potential effects of residual or unmeasured confounding factors.

Conclusion

Based on a large Norwegian birth cohort, we found that exposure to opioid analgesics in the first trimester and exposures in two to three 4-week intervals during pregnancy affected the literacy and numeracy skills of fifth-grade children, compared to fifth-grade children of mothers with only pre-pregnancy exposures. However, these associations were small in magnitude and the negative impact was not substantial. These findings are reassuring for pregnant women that need opioid analgesics for pain management. However, adequate pain management in pregnancy should be discussed on an individual patient level, bearing in mind the benefits and risks of different analgesic therapies.

Acknowledgements

The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study.
This work was supported by the European Research Council Starting Grant “DrugsInPregnancy” (grant no. 639377). EY was supported by the Research Council of Norway (grant no. 262177 and 288083). AL was supported by the Research Council of Norway (grant no. 288696)

References

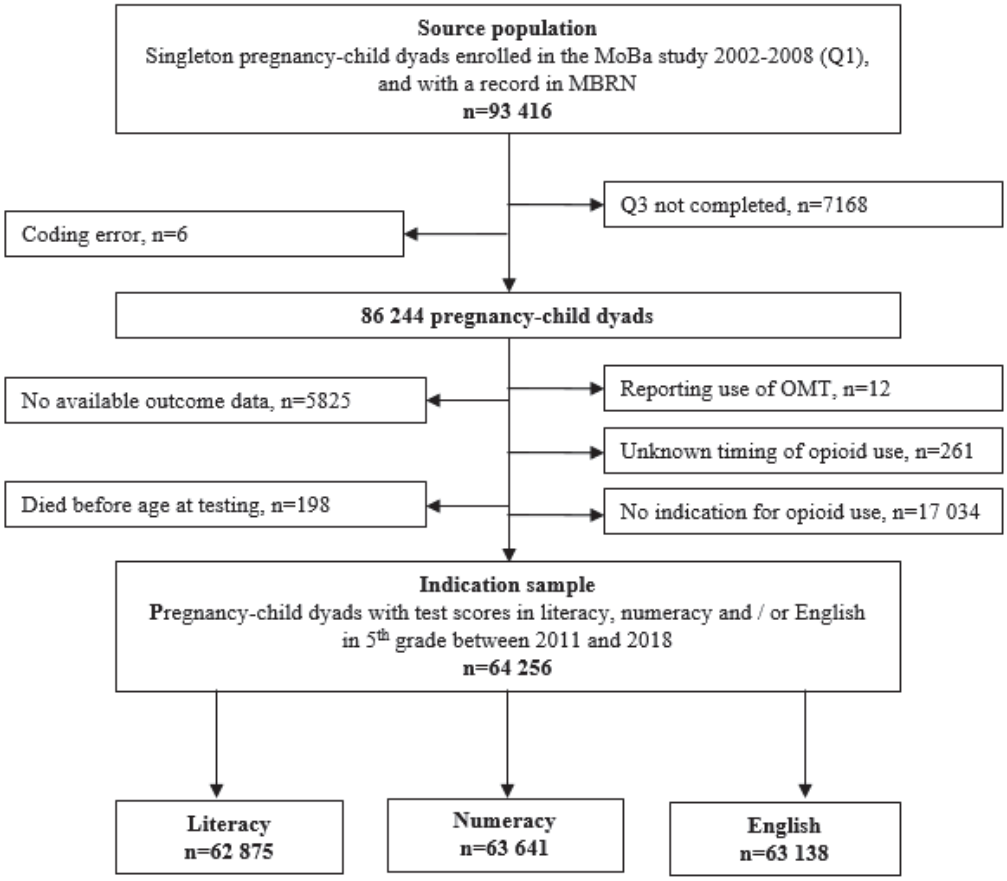
1. Engeland A, Bjorge T, Klungsoyr K, Hjellvik V, Skurtveit S, Furu K. Trends in prescription drug use during pregnancy and postpartum in Norway, 2005 to 2015. *Pharmacoepidemiol Drug Saf.* 2018;27(9):995-1004.
2. Sujan AC, Quinn PD, Rickert ME, et al. A nation-wide Swedish study of opioid analgesic prescribing patterns during pregnancy and associated preexisting mental health conditions. *J Matern Fetal Neonatal Med.* 2021:1-7.
3. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol.* 2014;123(5):997-1002.
4. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology.* 2014;120(5):1216-1224.
5. Ross EJ, Graham DL, Money KM, Stanwood GD. Developmental consequences of fetal exposure to drugs: what we know and what we still must learn. *Neuropsychopharmacol.* 2015;40(1):61-87.
6. Goldfarb SS, Stanwood GD, Flynn HA, Graham DL. Developmental opioid exposures: neurobiological underpinnings, behavioral impacts, and policy implications. *Exp Biol Med (Maywood).* 2020;245(2):131-137.
7. Boggess T, Risher WC. Clinical and basic research investigations into the long-term effects of prenatal opioid exposure on brain development. *J Neurosci Res.* 2020.
8. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: a comprehensive overview. *Curr Pain Headache Rep.* 2018;22(3):16.
9. Hjorth S, Bromley R, Ystrom E, Lupattelli A, Spigset O, Nordeng H. Use and validity of child neurodevelopment outcome measures in studies on prenatal exposure to psychotropic and analgesic medications - A systematic review. *PLoS One.* 2019;14(7):e0219778.
10. Wen X, Lawal OD, Belviso N, et al. Association between prenatal opioid exposure and neurodevelopmental outcomes in early childhood: a retrospective cohort study. *Drug Saf.* 2021;44(8):863-875.
11. Trønnes JN, Lupattelli A, Handal M, Skurtveit S, Ystrom E, Nordeng H. Association of timing and duration of prenatal analgesic opioid exposure with attention-deficit/hyperactivity disorder in children. *JAMA Netw Open.* 2021;4(9):e2124324.
12. Skovlund E, Handal M, Selmer R, Brandlistuen RE, Skurtveit S. Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. *Pharmacoepidemiol Drug Saf.* 2017;26(6):625-634.
13. Skovlund E, Selmer R, Skurtveit S, Brandlistuen RE, Handal M. In utero exposure to analgesic opioids and language development in 5-year old children. *Pharmacoepidemiol Drug Saf.* 2020;29(6):736-744.
14. Brown AS, Gyllenberg D, Malm H, et al. Association of selective serotonin reuptake inhibitor exposure during pregnancy with speech, scholastic, and motor disorders in offspring. *JAMA Psychiatry.* 2016;73(11):1163-1170.
15. Elkjær LS, Bech BH, Sun Y, Laursen TM, Christensen J. Association between prenatal valproate exposure and performance on standardized language and mathematics tests in school-aged children. *JAMA Neurol.* 2018;75(6):663-671.

16. Christensen J, Trabjerg BB, Sun Y, Dreier JW. Association of maternal antidepressant prescription during pregnancy with standardized test scores of Danish school-aged children. *JAMA.* 2021;326(17):1725-1735.
17. Titz C, Karbach J. Working memory and executive functions: effects of training on academic achievement. *Psychol Res.* 2014;78(6):852-868.
18. Duncan GJ, Dowsett CJ, Claessens A, et al. School readiness and later achievement. *Dev Psychol.* 2007;43(6):1428-1446.
19. Ritchie SJ, Bates TC. Enduring links from childhood mathematics and reading achievement to adult socioeconomic status. *Psychol Sci.* 2013;24(7):1301-1308.
20. Magnus P, Birke C, Vejrup K, et al. Cohort profile update: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol.* 2016;45(2):382-388.
21. Irgens LM. The Medical Birth Registry of Norway; a source for epidemiological and clinical research. *Scand J Rheumatol Suppl.* 1998;107:105-108.
22. Statistics Norway. https://www.ssb.no/en/. Accessed March 1, 2021.
23. WHO. WHO Collaborating Centre for Drug Statistics Methodology - ATC/DDD Index https://www.whocc.no/atc_ddd_index/. Accessed May 4, 2021.
24. The Norwegian Directorate for Education and Training. Kva er nasjonale prøver? . https://www.udir.no/eksamen-og-prover/prover/nasjonale-prover/om-nasjonale-prover/. Accessed November 12, 2021.
25. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011;22(5):745.
26. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol.* 2008;8:70.
27. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry.* 2003;57(2):113-118.
28. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behavioral Research* 2011;46(3):399-424.
29. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *Am J Epidemiol.* 2006;163(12):1149-1156.
30. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. *Psychol Methods.* 2010;15(3):234-249.
31. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.
32. Lupattelli A, Wood ME, Nordeng H. Analyzing missing data in perinatal pharmacoepidemiology research: methodological considerations to limit the risk of bias. *Clin Ther.* 2019;41(12):2477-2487.
33. Harel O, Mitchell EM, Perkins NJ, et al. Multiple imputation for incomplete data in epidemiologic studies. *Am J Epidemiol.* 2018;187(3):576-584.
34. Mitra R, Reiter JP. A comparison of two methods of estimating propensity scores after multiple imputation. *Stat Methods Med Res.* 2016;25(1):188-204.
35. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med.* 2019;38(26):5120-5132.

36. Wood ME, Andrade SE, Toh S. Safe expectations: current state and future directions for medication safety in pregnancy research. *Clin Ther.* 2019;41(12):2467-2476.
37. Schaefer C, Peters P, Miller RK. Drugs during pregnancy and lactation. Treatment options and risk assessment. London: Academic Press; 2015.
38. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev.* 2003;27(1-2):3-18.
39. Knight J, Cassell CH, Meyer RE, Strauss RP. Academic outcomes of children with isolated orofacial clefts compared with children without a major birth defect. *Cleft Palate Craniofac J.* 2015;52(3):259-268.
40. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA.* 2002;288(6):728-737.
41. Bateman BT, Hernandez-Diaz S, Straub L, et al. Association of first trimester prescription opioid use with congenital malformations in the offspring: population based cohort study. *Bmj.* 2021;372:n102.
42. Brogly SB, Velez MP, Werler MM, Li W, Camden A, Guttmann A. Prenatal opioid analgesics and the risk of adverse birth outcomes. *Epidemiology.* 2021;32(3):448-456.
43. Sujan AC, Quinn PD, Rickert ME, et al. Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: a population-based study. *PLoS Med.* 2019;16(12):e1002980.
44. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. *Obstet Gynecol.* 2013;122(4):838-844.
45. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol.* 2011;204(4):314.e311-311.
46. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *Eur J Clin Pharmacol.* 2011;67(12):1253-1261.
47. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med.* 2014;275(6):570-580.
48. Cohen J. Statistical power analysis for the behavioral sicences. 2nd ed. NJ: Lawrence Erlbaum Associates: Hillsdale; 1988.
49. Magnusson K. Interpreting Cohen's d effect size—an interactive visualization. https://rpsychologist.com/cohend/. Accessed November 10, 2021.
50. Borenstein M, Hedges LV, Higgins JPT, Rothstein H. Introduction to meta-analysis. 2nd ed. Chickester, West Sussex, U.K.: John Wiley & Sons; 2009.
51. Guidelines for pain management. The Norwegian Medical Association. https://www.legeforeningen.no/om-oss/publikasjoner/retningslinjer/retningslinjer-for-smertelindring-2009/, Accessed November 26, 2018.
52. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
53. Källen K, Wide K. Kodein. Fosterpåverkan | Janusmed. 2018. https://janusmed.sll.se/fosterpaverkan Accessed November 10, 2021.
54. Desai RJ, Huybrechts KF, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. *Bmj.* 2015;350:h2102.

55. Bromley RL, Baker GA. Fetal antiepileptic drug exposure and cognitive outcomes. *Seizure.* 2017;44:225-231.
56. Maughan B, Rowe R, Loeber R, Stouthamer-Loeber M. Reading problems and depressed mood. *J Abnorm Child Psychol.* 2003;31(2):219-229.
57. Yeoh SL, Eastwood J, Wright IM, et al. Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis. *JAMA Netw Open.* 2019;2(7):e197025.
58. Larson JJ, Graham DL, Singer LT, et al. Cognitive and behavioral impact on children exposed to opioids during pregnancy. *Pediatrics.* 2019;144(2).
59. Mahic M, Hernandez-Diaz S, Wood M, et al. In utero opioid exposure and risk of infections in childhood: a multinational Nordic cohort study. *Pharmacoepidemiol Drug Saf.* 2020;29(12):1596-1604.
60. Mravčík V, Nechanská B, Gabrhelík R, Handal M, Mahic M, Skurtveit S. Socioeconomic characteristics of women with substance use disorder during pregnancy and neonatal outcomes in their newborns: a national registry study from the Czech Republic. *Drug Alcohol Depend.* 2020;209:107933.
61. 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.
62. Biele G, Gustavson K, Czajkowski NO, et al. Bias from self selection and loss to follow-up in prospective cohort studies. *Eur J Epidemiol.* 2019;34(10):927-938.
63. Ruijsbroek A, Wijga AH, Gehring U, Kerkhof M, Droomers M. School performance: a matter of health or socio-economic background? Findings from the PIAMA Birth Cohort Study. *PLoS One.* 2015;10(8):e0134780.
64. Meador KJ, Baker GA, Browning N, et al. Relationship of child IQ to parental IQ and education in children with fetal antiepileptic drug exposure. *Epilepsy Behav.* 2011;21(2):147-152.
65. Raffa RB, Pergolizzi JV, Jr. A modern analgesics pain 'pyramid'. *J Clin Pharm Ther.* 2014;39(1):4-6.

Figure 1. Flowchart to achieve study samples



*MoBa children born in 1999-2001 were not included in the study due to lack of consent, as they turned 18 before the follow-up were complete in 2018.
Conditions of exclusion can overlap.
OMT: Opioid Maintenance Treatment, women reporting use of drugs with ATC code N07BC.
MoBa: The Norwegian Mother, Father and Child Cohort Study
MBRN: The Medical Birth Registry of Norway

495 **Table 1.** Characteristics of the study sample according to prenatal opioid exposure status (n=64 256)

	Exposure status		
	Exposed n=1483 N (%)	**Pre-pregnancy exposed only n=731 N (%)**	**Unexposed n=62 042 N (%)**
Maternal characteristics[†]			
Age at delivery			
<25	155 (10.4)	107 (14.6)	7075 (11.4)
25-29	473 (31.9)	241 (32.9)	21 041 (33.9)
30-34	554 (37.4)	271 (37.1)	23 794 (38.4)
≥35	301 (20.3)	112 (15.4)	10 132 (16.3)
Marital status			
Married / cohabitant	1410 (95.1)	697 (95.4)	59 865 (96.5)
Other	66 (4.4)	30 (4.1)	1876 (3.0)
Parity			
Primiparous	607 (40.9)	400 (54.7)	27 878 (44.9)
Multiparous (?)	876 (59.1)	331 (45.3)	34 164 (55.1)
Education level[a]			
10 year primary school or less	168 (11.3)	81 (11.1)	4955 (8.0)
Secondary / vocational school	476 (32.1)	242 (33.1)	17 749 (28.6)
BA/MA/PhD	835 (56.3)	405 (55.4)	38 912 (62.7)
Familiy income[b]			
ITNR <2	590 (39.8)	290 (39.7)	22 069 (35.6)
ITNR 2-3	689 (46.5)	313 (42.8)	28 876 (46.5)
ITNR ≥3	194 (13.1)	123 (16.8)	10 469 (16.9)
Prepregnancy BMI, mean (SD)	25.1 ± 4.9	24.8 ± 4.7	24.1 ± 4.3
Smoking[c]			
No	1033 (69.6)	506 (69.2)	46 083 (74.2)
Yes	213 (14.3)	111 (15.2)	5795 (9.3)
Alcohol[d]			
No	1261 (85.0)	648 (88.6)	54 775 (88.2)
Yes	52 (3.5)	19 (2.6)	1449 (2.3)
Symptoms of anxiety/depression[e], mean score (SD)	1.4 ± 0.5	1.4 ± 0.4	1.3 ± 0.4
Maternal chronic disease[f]			
No	1188 (80.1)	585 (80.0)	53 917 (86.9)
Yes	295 (19.9)	146 (20.0)	8125 (13.1)
Use of co-medication[d]			
Paracetamol	728 (49.1)	238 (32.6)	17 811 (28.7)
Triptans	80 (5.4)	5 (0.7)	475 (0.8)
NSAIDs	210 (14.2)	42 (5.8)	2783 (4.5)
Antidepressant	39 (2.6)	11 (1.5)	588 (1.0)
Benzodiazepines and BDZ-like drugs	46 (3.1)	5 (0.7)	252 (0.4)
Antiepileptic	10 (0.7)	4 (0.6)	186 (0.3)
Anti-psychotic	22 (1.5)	8 (1.1)	368 (0.6)
Number of pain types reported during pregnancy			
1	224 (15.1)	86 (11.8)	16 322 (26.3)
2-3	502 (33.9)	286 (39.1)	27 530 (44.4)
4 or more	757 (51.0)	359 (49.1)	18 190 (29.3)
Child characteristics			
Boys	740 (49.9)	359 (49.1)	31 422 (50.7)

Preterm (<37 weeks)	99 (6.7)	35 (4.8)	2644 (4.3)
Time of year the baby was born			
January-June	775 (52.3)	381 (52.1)	31 592 (50.9)
July-December	708 (47.7)	350 (47.9)	30 450 (49.1)
Paternal Characteristics			
Age			
25-29	398 (26.8)	231 (31.6)	17 516 (28.1)
30-34	568 (38.3)	263 (35.9)	24 159 (38.9)
≥ 35	514 (34.7)	236 (32.3)	20 235 (32.6)
Education level[a]			
10 year primary school or less	199 (13.4)	116 (15.9)	6813 (11.0)
Secondary / vocational school	688 (46.4)	320 (43.8)	26 597 (42.9)
BA/MA/PhD	583 (39.3)	285 (38.9)	27 831 (44.8)

Abbrevations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ITNR, Income to needs ratio; BA, Bachelor's degree; MA; Master's degree.

[†] Numbers may not add up to 100% due to missing values, marital status (0.5%), maternal education level (0.7%), family income (1.0%), BMI (2.5%), smoking (16.4%), alcohol (9.4%), symptoms of anxiety and depression (3.4%), premature birth (0.4%), paternal age (0.2%), paternal education level (1.3%).

[a)] Education level was reported in the child's birth year.

[b)] Family income was assessed by income-to-needs-ratio (ITNR, EU-60) reported in the year prior to childbirth.

[c)] Smoking status was reported at the start of pregnancy.

[d)] Measured in the first MoBa questionnaire.

[e)] Symptoms of anxiety/depression was measured by a short version of the Hopkins Symptom Checklist (SCL-5) in the first MoBa questionnaire.

[f)] Maternal chronic disease include the following: asthma, diabetes, hypertension, other heart disease, epilepsy, thyroid disorder or arthritis reported in the period 6 months prior to pregnancy.

498 **Table 2.** Association between timing and duration of prenatal exposure to opioid analgesics and scholastic skills
499 among children in fifth grade, with children of mothers with pre-pregnancy exposure only as comparator.

Literacy				
	N	**Mean z score (SD)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Prepregnancy exposure only	721	0.21 (1.0)	Reference	Reference
Exposed	1445	0.15 (1.0)	-0.06 (-0.15, 0.03)	-0.06 (-0.16, 0.04)
By timing of exposure				
1st trimester	671	0.09 (1.0)	-0.12 (-0.23, -0.02)	-0.13 (-0.25, -0.01)
2nd trimester	783	0.17 (1.0)	-0.04 (-0.14, 0.05)	-0.05 (-0.16, 0.05)
3rd trimester	486	0.18 (1.0)	-0.04 (-0.14, 0.07)	-0.03 (-0.15, 0.09)
By duration of exposure				
1 interval	917	0.18 (1.0)	-0.03 (-0.13, 0.06)	-0.03 (-0.13, 0.07)
2-3 intervals	313	0.09 (1.0)	-0.13 (-0.26, -0.00)	-0.19 (-0.35, -0 04)
≥4 intervals	215	0.12 (1.0)	-0.09 (-0.24, 0.06)	-0.02 (-0.21, 0.16)
Numeracy				
	N	**Mean z score (SD)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Prepregnancy exposure only	722	0.21 (1.0)	Reference	Reference
Exposed	1469	0.11 (1.0)	-0.09 (-0.18, -0.01)	-0.08 (-0.17, 0.01)
By timing of exposure				
1st trimester	677	0.05 (1.0)	-0.16 (-0.26, -0.06)	-0.14 (-0.25, -0.04)
2nd trimester	800	0.15 (1.0)	-0.06 (-0.15, 0.04)	-0.06 (-0.16, 0.04)
3rd trimester	492	0.13 (1.0)	-0.08 (-0.18, 0.04)	-0.05 (-0.18, 0.07)
By duration of exposure				
1 interval	929	0.14 (1.0)	-0.07 (-0.16, 0.03)	-0.06 (-0.16, 0.03)
2-3 intervals	322	0.05 (1.0)	-0.16 (-0.29, -0.03)	-0.19 (-0.34, -0.05)
≥4 intervals	218	0.10 (1.0)	-0.10 (-0.25, 0.04)	-0.05 (-0.25, 0.14)
English				
	N	**Mean z score (SD)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Prepregnancy exposure only	718	0.07 (1.0)	Reference	Reference
Exposed	1444	0.08 (1.0)	-0.02 (-0.11, 0.07)	-0.04 (-0.13, 0.06)
By timing of exposure				
1st trimester	672	0.01 (1.0)	-0.06 (-0.17, 0.04)	-0.06 (-0.17, 0.06)
2nd trimester	780	0.08 (1.0)	0.01 (-0.09, 0.11)	-0.02 (-0.13, 0.09)
3rd trimester	484	0.08 (1.0)	0.01 (-0.11, 0.12)	-0.02 (-0.15, 0.10)
By duration of exposure				
1 interval	917	0.05 (1.0)	-0.02 (-0.12, 0.08)	-0.03 (-0.13, 0.06)
2-3 intervals	313	0.01 (1.0)	-0.07 (-0.20, 0.07)	-0.11 (-0.26, 0.05)
≥4 intervals	214	0.11 (1.0)	0.04 (-0.12, 0.19)	0.12 (-0.10, 0.35)

β: indicates standardized mean difference in test scores
1 interval corresponds to a 4-week period, but not necessarily consecutive use in that period.

500

Table 3. Association between timing and duration of prenatal exposure to opioid analgesics and scholastic skills among children in fifth grade, with unexposed children as comparator.

Literacy				
	N	**Mean z score (SD)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Unexposed	60 709	0.21 (1.0)	Reference	Reference
Exposed	1445	0.15 (1.0)	-0.05 (-0.10, 0.00)	-0.01 (-0.06, 0.04)
By timing of exposure				
1st trimester	671	0.09 (1.0)	-0.12 (-0.19, -0.04)	-0.06 (-0.14, 0.01)
2nd trimester	783	0.17 (1.0)	-0.04 (-0.11, 0.03)	0.01 (-0.06, 0.08)
3rd trimester	486	0.18 (1.0)	-0.03 (-0.11, 0.06)	0.00 (-0.09, 0.08)
By duration of exposure				
1 interval	917	0.18 (1.0)	-0.02 (-0.09, 0.04)	0.02 (-0.04, 0.08)
2-3 intervals	313	0.09 (1.0)	-0.13 (-0.23, -0.02)	-0.09 (-0.20, 0.02)
≥4 intervals	215	0.12 (1.0)	-0.08 (-0.21, 0.04)	0.01 (-0.11, 0.14)
Numeracy				
	N	**Mean z score (SD)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Unexposed	61 450	0.20 (1.0)	Reference	Reference
Exposed	1469	0.11 (0.1)	-0.09 (-0.14, -0.04)	-0.02 (-0.07, 0.03)
By timing of exposure				
1st trimester	677	0.05 (1.0)	-0.15 (-0.23, -0.08)	-0.06 (-0.13, 0.02)
2nd trimester	800	0.15 (1.0)	-0.05 (-0.12, 0.02)	0.01 (-0.06, 0.08)
3rd trimester	492	0.13 (1.0)	-0.07 (-0.16, 0.02)	0.00 (-0.08, 0.09)
By duration of exposure				
1 interval	929	0.14 (1.0)	-0.06 (-0.13, 0.00)	-0.01 (-0.07, 0.06)
2-3 intervals	322	0.05 (1.0)	-0.16 (-0.27, -0.05)	-0.11 (-0.22, 0.01)
≥4 intervals	218	0.10 (1.0)	-0.10 (-0.23, 0.02)	0.03 (-0.09, 0.16)
English				
	N	**Mean z score (SD)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Unexposed	60 976	0.08 (1.0)	Reference	Reference
Exposed	1444	0.05 (1.0)	-0.03 (-0.08, 0.02)	-0.01 (-0.07, 0.04)
By timing of exposure				
1st trimester	672	0.01 (1.0)	-0.07 (-0.14, 0.01)	-0.03 (-0.11, 0.04)
2nd trimester	780	0.08 (1.0)	0.00 (-0.07, 0.07)	0.00 (-0.07, 0.08)
3rd trimester	484	0.08 (1.0)	0.00 (-0.09, 0.09)	0.00 (-0.08, 0.09)
By duration of exposure				
1 interval	917	0.05 (1.0)	-0.03 (-0.09, 0.04)	-0.01 (-0.07, 0.06)
2-3 intervals	313	0.01 (1.0)	-0.07 (-0.19, 0.04)	-0.08 (-0.19, 0.04)
≥4 intervals	214	0.11 (1.0)	0.03 (-0.10, 0.16)	0.06 (-0.08, 0.20)

β: indicates standardized mean difference in test scores
1 interval corresponds to a 4-week period, but not necessarily consecutive use in that period.

Supplementary Online Content

Trønnes JN, Lupattelli A, Ystrom E, Nordeng H. Prenatal exposure to opioid analgesics and scholastic skills in fifth grade – a follow up study in the Norwegian Mother, Father, and Child Cohort.

List of eTables and eFigures

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

eMethods

Study sample:
The MoBa study recruited pregnant women between 1999-2008, however, they youngest children, born in the period 1999-2001, could not be included in the study due to lack of consent as they turned 18 before the end of follow- up in 2018.

Outcome:
National tests were introduced in Norway as part of the national quality assessment system in 2004, however, tests have been performed every year since 2007. National tests are mandatory, and only pupils with special needs are exempted. National tests are held in the first semester of the fifth, eight, and ninth grade and test the basic skills of reading/literacy, numeracy, and English language. The pupils perform the tests on computers and have 90 minutes to complete one test. The tests are scored from zero and upwards.[1] eTable 2 and eTable 3 shows a simple comparison of scores between the MoBa participants and the complete population of test takers in each subject and each test year. eFigure 1 shows the distribution of scores in literacy, numeracy and English. Below is a more thorough description of what is being tested in each subject.

Literacy[1]
Reading and language is arguably the most important academic skill learned in school. The reading test is done by presenting the student with a text (roughly an A4 sheet 12pt text) and then asking multiple-choice questions in different complexity about the text. This measures speed of reading as well as the ability to decompose a longer segment of coherent text. The exams are designed to test for the following abilities: to find information in a text, to interpret a text, and to reflect and evaluate the content of a text. While volume training and exposure are important for most scholastic skills, this is especially important for reading. Volume training by reading different materials and books of increasing complexity is the primary way of excelling in reading and reflecting over writing content. The raw test scores range between a minimum of 0 points to a maximum of 34 points.

Numeracy[1]
Unlike reading, high volume and exposure is not sufficient for excelling in mathematics, with large volume being potentially detrimental to performance. The test should reflect multiple sub-domains in mathematics, such as numeracy, geometry, and statistics. Numeracy is the basics of number manipulation, but is limited to as addition, subtraction, multiplication, and division. Geometry and measurements, are the two and three dimensional representations of numeracy, where comparing volumes and surfaces of different measurements are evaluated. Statistics is operationalized as a visualization of data, mostly into charts and diagrams, with some data summary, such as mean, median, and factors. The raw test scores range between a minimum of 0 points to a maximum of 45 points.

English[1]
The tests are designed to measure three different aspects of English language; general reading, vocabulary and grammar. The raw test scores range between a minimum of 0 points to a maximum of 50 points.

Covariates:
Family income was assessed by income-to-needs-ratio (ITNR), which is family income after tax divided by the poverty level i.e. consumption equivalents. The EU-60 standard was applied.[2] The higher ITNR level, the better off are the family. ITNR was grouped into 3 levels (ITNR <2, ITNR 2-3, ITNR≥3). ITNR was assessed one year prior to childbirth.

Statistical analysis:
In a sub-analysis, we used unexposed children as reference group. For this analysis we used propensity scores with standardized mortality/morbidity ratio weights (SMR), instead of inverse probability of treatment (IPT) weights as were used in the main analysis with discontinuers. According to Stürmer et. al.[3] SMR weights are preferred when we have an unexposed reference group or when the reference group is not well defined. However, when we have an active reference (or disease comparator), the inverse probability of treatment (IPT) weights can be used. This is because with an active reference, we assume that the prevalence of the indication for treatment is somewhat similar

between the two groups, thus reducing the potential for violations of the positivity assumption.[4] Then it would make sense to estimate the average treatment effect in the entire population and thus IPT weights can be used. IPT weights creates a pseudo-population of both the exposed and unexposed, which has the same covariate distribution as the overall population of exposed and unexposed. Every person is weighted by the inverse of the probability of receiving the treatment actually received. This answers the question: "what would have happened if everyone had been exposed versus what would have happened if everyone had not been exposed?" Standardized mortality/morbidity ratio (SMR) weights creates a pseudo-population of the unexposed, which has the same covariate distribution as the exposed. Every exposed person receives the weight of 1, while the unexposed are down-weighted and receives the weight of PS odds (PS/1-PS). With the SMR weights, we estimate the average treatment effect in the treated, which answers the question "what would have happened if those actually exposed had not been exposed?".

Subanalyses and sensitivity analyses:
In a sensitivity analysis, we compared children exposed to opioid analgesics in one period with children exposed in 2 or more intervals during pregnancy in order to examine associations with length of exposure.
In a sensitivity analysis, we used an alternative model specification (cf. eTable 6). Use of co-medications was measured in the period 6 months before pregnancy, and we removed symptoms of depression and anxiety measured in gestational week 17.
In the last sensitivity analysis, we restricted the study sample to women who had returned the MoBa questionnaire at 6 months post-partum (MoBa Q4), to ensure that every women had complete information on exposure, repeated our main analysis.

eResults

Results of sensitivity analyses
Children exposed to opioid analgesics in one interval scored similar to those exposed in two intervals or more during pregnancy (eTable 11).

In the analysis with the alternative model specification, point estimates did not differ substantially from the main analysis (data not shown). However, only associations of prenatal exposure in first trimester and in 2-3 4-week intervals with lower scores on the numeracy test remained significant. No other associations were found.

When MoBa Q4-returned was required to enter the study sample, the sample included 57 954 pregnancies. The point estimates were similar to those reported in the main analysis and conclusions remain the same (Data not shown).

eTable 1. Relevant indications for opioid use during pregnancy

Indications	MoBa Q1	MoBa Q3
Pelvic girdle pain	X	X
Abdominal pain	X	
Back pain	X	X
Neck and shoulder	X	
Arthritis	X	
Sciatica	X	
Fibromyalgia	X	
Other pains in muscles/joints		X
Migraine	X	
Other headache	X	
Headache / migraine		X

Abbrevations: MoBa, The Norwegian Mother, Father and Child Cohort; Q1, the first MoBa questionnaire; Q3, the third MoBa questionnaire.

eTable 2. Test scores among children in MoBa and all children in Norway who took the test, according to subject and test year.

	Year	MoBa children (n=93 416)		General population	
		N	Raw scores, mean ± SD	N	Raw scores, mean ± SD
Literacy	2011	14	24.0 ± 3.4	54 826	21.3 ± 5.9
	2012	7434	19.3 ± 6.0	54 319	18.6 ± 6.2
	2013	10 869	22.4 ± 6.5	55 314	21.5 ± 6.7
	2014	11 707	19.7 ± 5.8	55 862	18.8 ± 6.1
	2015	13 484	21.5 ± 6.3	55 611	20.3 ± 6.5
	2016	15 421	20.1 ± 7.0	58 297	18.4 ± 7.1
	2017	14 197	20.7 ± 6.1	58 192	19.0 ± 6.4
	2018	11 822	19.1 ± 5.9	59 792	17.4 ± 6.1
	Overall	84 948	20.5 ± 6.4	452 213	19.4 ± 6.5
Numeracy	2011	14	30.1 ± 6.5	55 122	26.0 ± 8.5
	2012	7510	27.7 ± 8.4	54 790	26.7 ± 8.6
	2013	11 063	26.5 ± 9.1	56 298	25.2 ± 9.4
	2014	11932	25.5 ± 9.1	57 235	24.1 ± 9.3
	2015	13 818	25.5 ± 9.0	57 117	23.8 ± 9.6
	2016	15 500	25.5 ± 9.0	58 829	23.3 ± 9.2
	2017	14 246	25.2 ± 9.3	58 710	22.8 ± 9.5
	2018	11 897	27.6 ± 9.1	60 478	24.8 ± 9.5
	Overall	85 980	26.1 ± 9.2	458 579	24.6 ± 9.3
English	2011*	-	-	-	-
	2012	7445	27.7 ± 11.3	54 426	27.3 ± 11.4
	2013	10 996	27.9 ± 10.5	55 978	27.5 ± 10.6
	2014	11 829	27.5 ± 9.8	56 764	26.8 ± 10.0
	2015	13 723	26.8 ± 10.4	56 625	26.3 ± 10.6
	2016	15 365	26.6 ± 9.3	58 229	25.7 ± 9.5
	2017	14 142	27.4 ± 9.6	58 080	26.4 ± 9.8
	2018	11 788	27.4 ± 10.4	59 795	26.4 ± 10.7
	Overall	85 288	27.3 ± 10.1	399 897	26.6 ± 10.4

Abbrevations: MoBa, The Norwegian Mother, Father and Child cohort

* Due to large technical problems the Norwegian directorate of education and training cancelled national tests in English in 2011.[5]

eTable 3. National tests results of the MoBa children presented as z-scores.

	MoBa children, n=93 416		
Test subject	**N**	**Mean scores (SD)**	**Median scores (P25, P75)**
Literacy 5th grade	84 948	0.21 (0.97)	0.37 (-0.48, 0.97)
Numeracy 5th grade	85 980	0.20 (0.98)	0.23 (-0.54, 0.96)
English 5th grade	85 288	0.07 (0.98)	0.03 (-0.69, 0.88)

Abbrevations: MoBa, The Norwegian Mother, Father and Child cohort

P25 indicate the 25th percentile, and P75 indicate the 75th percentile of the z-score.

eTable 4. Overview of data source of covariates

Variable	Data Source
Maternal age	MBRN
Marital status	MoBa Q1
Parity	MBRN
Education level	SSB
Family income	SSB
Pre-pregnancy BMI	MoBa Q1
Smoking status at start of pregnancy	MBRN
Alcohol use	MoBa Q1
Symptoms of anxiety depression	MoBa Q1
Maternal chronic diseases before pregnancy	MoBa Q1
Co-medication -Paracetamol -Triptans -NSAIDS -Antidepressants -Benzodiazepine and benzodiazepine-like drugs -Antiepileptic -Anti-psychotics	MoBa Q1
Paternal age	MBRN
Paternal education	SSB
Child sex	MBRN
Time of year the baby was born	MBRN

Abbrevations: MBRN, The Medical Birth Registry of Norway; MoBa, The Norwegian Mother, Father and Child Cohort; SSB, Statistics Norway; Q1, The first MoBa questionnaire.

eTable 5. Characteristics of generated weights by exposure status compared to discontinuers

	Literacy		Numeracy		English	
	Estimated IPTW		Estimated IPTW		Estimated IPTW	
	Mean (SD)	**Min-Max**	**Mean (SD)**	**Min-Max**	**Mean (SD)**	**Min-Max**
Prepregnancy exposed	Reference	Reference	Reference	Reference	Reference	Reference
Exposed	1.0 (0.3)	0.6-5.6	1.0 (0.3)	0.6-5.3	1.0 (0.3)	0.6-5-8
Timing of exposure						
1st trimester	1.0 (0.5)	0.5-9.7	1.0 (0.6)	0.5-8.4	1.0 (0.5)	0.5-9.7
2nd trimester	1.0 (0.3)	0.5-4.8	1.0 (0.3)	0.5-5.6	1.0 (0.4)	0.5-6.4
3rd trimester	1.0 (0.4)	0.4-5.4	1.0 (0.4)	0.4-5.1	1.0 (0.4)	0.4-6.2
Duration of exposure						
1 interval	1.0 (0.2)	0.6-3.3	1.0 (0.2)	0.6-3.0	1.0 (0.2)	0.6-3.0
2-3 intervals	1.0 (0.4)	0.3-4.9	1.0 (0.4)	0.3-4.7	1.0 (0.4)	0.3-4.8
4 or more intervals	1.0 (0.6)	0.2-11.2	0.9 (0.7)	0.2-13.6	1.0 (0.7)	0.2-16.2

Abbreviations: IPTW, Inverse probability of treatment weights; SD, Standard deviation.

eTable 6. Overview of alternative model specifications

	Model	Description
Main	1	**sIPTW:** **Numerator:** Probability of exposure. **Denominator:** Maternal age, marital status, parity, maternal and paternal education level (in birth year), family income-to-needs-ratio (1 year prior to child birth), pre-pregnancy BMI, chronic disease pp, alcohol use (Q1), smoking habits at pregnancy start, use of co-medications (Q1), symptoms of anxiety and depression (SCL-5, Q1), time of year born (before/after summer) and paternal age.
Alternative model	2	**sIPTW:** **Numerator:** Probability of exposure. **Denominator:** Maternal age, marital status, parity, maternal and paternal education level (in birth year), family income-to-needs-ratio (1 year prior to child birth), pre-pregnancy BMI, chronic disease pp, smoking habits at pregnancy start, use of co-medications (pp), time of year born (before/after summer) and paternal age. In this model, all covariates included are measured before pregnancy.

eTable 7. Role of gender on scholastic skills in fifth grade according to exposure status.

		Boys			Girls		
		N	**Crude β (95% CI)**	**Weighted β (95% CI)**	**N**	**Crude β (95% CI)**	**Weighted β (95% CI)**
LITERACY SAMPLE	Pre-pregnancy exposed	353	Reference	Reference	368	Reference	Reference
	Exposed	717	-0.05 (-0.18, 0.08)	-0.04 (-0.19, 0.11)	728	-0.07 (-0.18, 0.05)	-0.08 (-0.20, 0.04)
	Unexposed	30 608	Reference	Reference	30 101	Reference	Reference
	Exposed	717	-0.04 (-0.11, 0.04)	0.01 (-0.06, 0.09)	728	-0.07 (-0.14, -0.01)	-0.03 (-0.10, 0.04)
NUMERACY SAMPLE		**N**	**Crude β (95% CI)**	**Weighted β (95% CI)**	**N**	**Crude β (95% CI)**	**Weighted β (95% CI)**
	Pre-pregnancy exposed	354	Reference	Reference	368	Reference	Reference
	Exposed	731	-0.07 (-0.20, 0.05)	-0.06 (-0.19, 0.08)	738	-0.11 (-0.23, 0.002)	-0.10 (-0.22, 0.01)
	Unexposed	31 125	Reference	Reference	30 325	Reference	Reference
	Exposed	731	-0.04 (-0.12, 0.03)	0.02 (-0.05, 0.10)	738	-0.13 (-0.20, -0.06)	-0.06 (-0.13, 0.01)
ENLIGH SAMPLE		**N**	**Crude β (95% CI)**	**Weighted β (95% CI)**	**N**	**Crude β (95% CI)**	**Weighted β (95% CI)**
	Pre-pregnancy exposed	353	Reference	Reference	365	Reference	Reference
	Exposed	718	-0.003 (-0.14, 0.13)	-0.03 (-0.17, 0 12)	726	-0.04 (-0.16, 0.08)	-0.05 (-0.18, 0.07)
	Unexposed	30 765	Reference	Reference	30 211	Reference	Reference
	Exposed	718	0.02 (-0.06, 0.09)	0.04 (-0.04, 0.11)	726	-0.08 (-0.14, -0.01)	-0.06 (-0.13, 0.01)

β: indicates standardized mean difference in test scores.

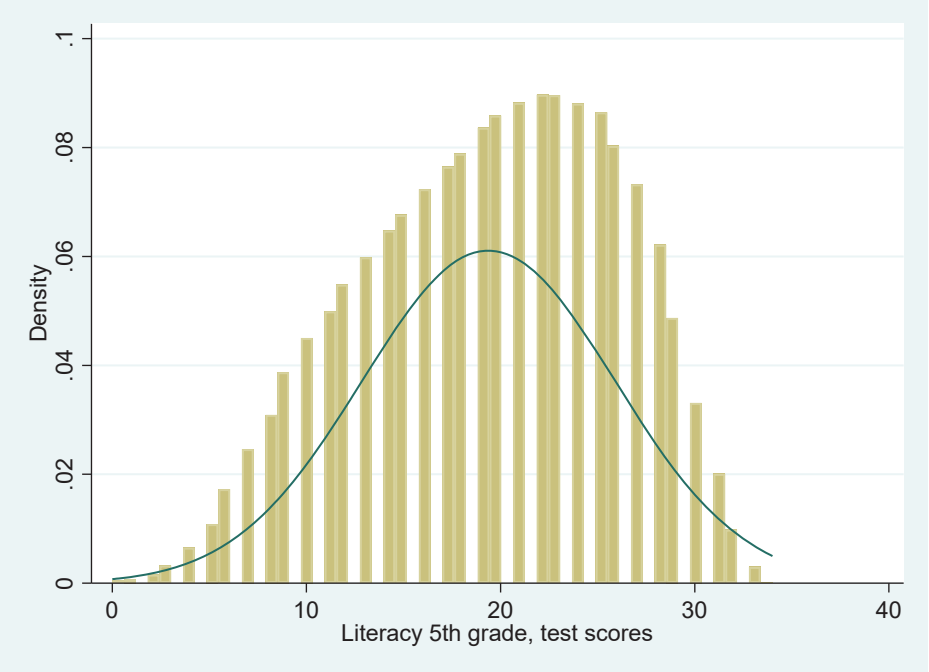
eTable 8. Association between duration of prenatal exposure to opioid analgesics and scholastic skills in fifth grade.

		Literacy		Numeracy		English	
	N	**Crude β (95% CI)**	**Weighted β (95% CI)**	**Crude β (95% CI)**	**Weighted β (95% CI)**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Exposed in 1 interval	917	Reference	Reference	Reference	Reference	Reference	Reference
Exposed in 2 or more intervals	527	-0.08 (-0.19, 0.02)	-0.09 (-0.20, 0.02)	-0.07 (-0.18, 0.03)	-0.06 (-0.17, 0.05)	-0.01 (-0.11, 0.10)	-0.03 (-0.14, 0.09)

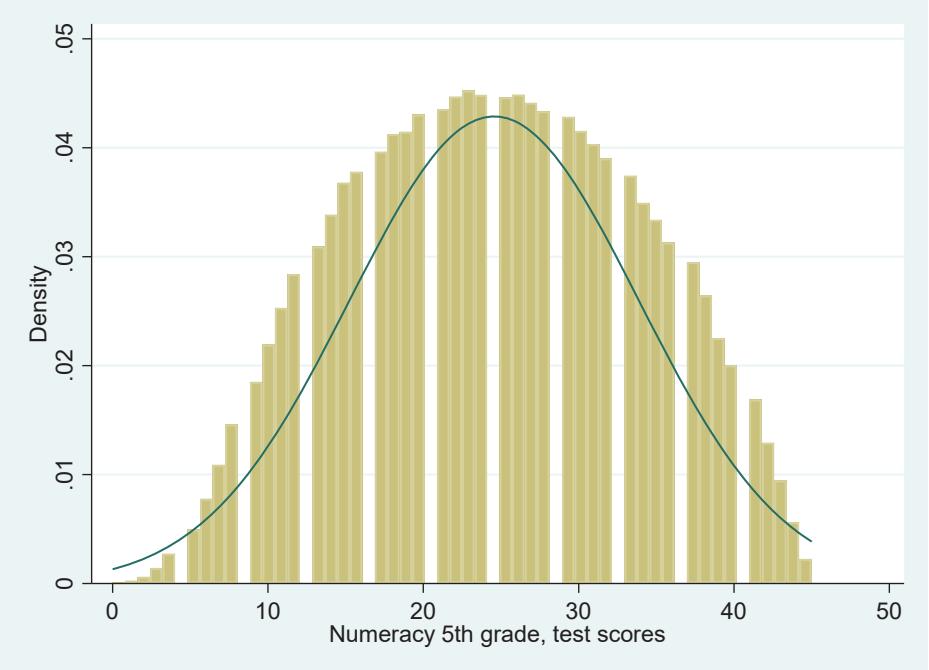
β: indicates standardized mean difference in test scores

11

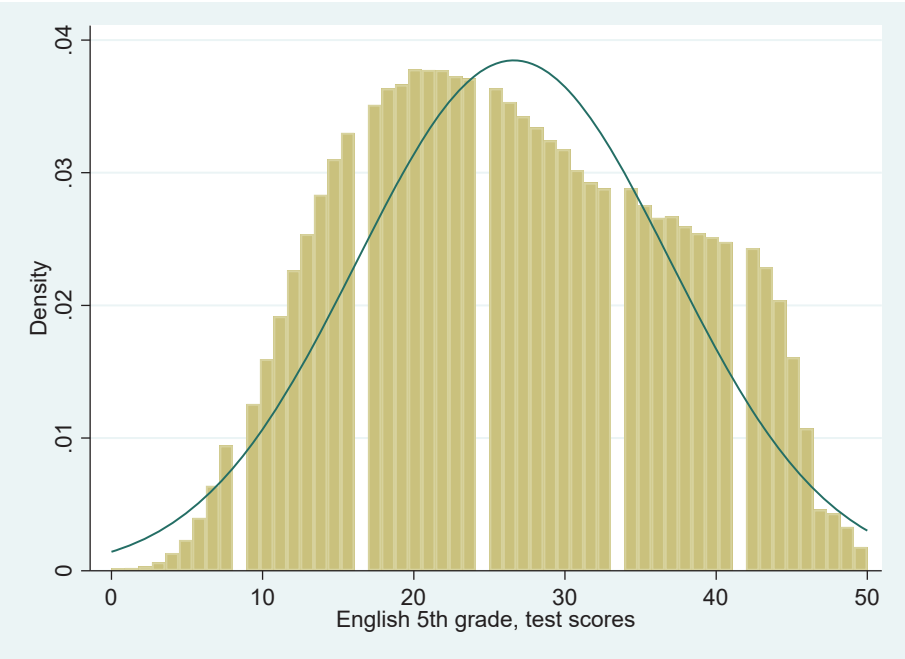
eFigure 1. Distribution of test scores in the complete population of test takers in fifth grade between 2011 and 2018, according to subject (A, B, C).



A) Test scores on the literacy test.
Mean (SD): 19.4 ± 6.5
Median (Range): 20 (0-34)

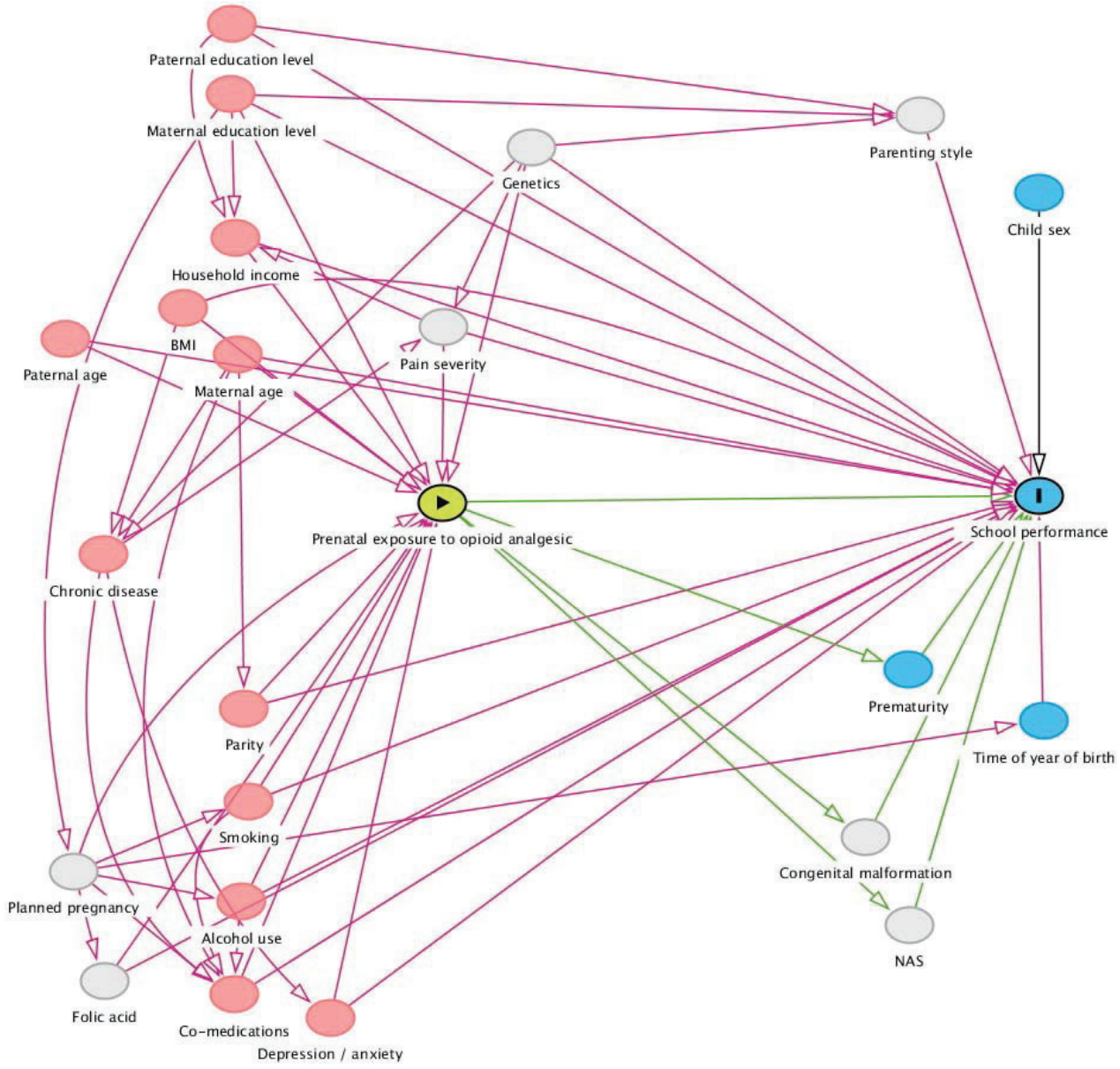


B) Test scores on the numeracy test
Mean (SD): 24.6 ± 9.3
Median (Range): 25 (0-45)



C) Test scores on the English test
Mean (SD): 26.6 ± 10.4
Median (Range): 26 (0-50)

eFigure 2. Simplified directed acyclic graph showing assumed covariate structure.



Abbreviations: NAS, neonatal abstinence syndrome; BMI, body mass index.

References

1. The Norwegian Directorate for Education and Training. Kva er nasjonale prøver? . https://www.udir.no/eksamen-og-prover/prover/nasjonale-prover/om-nasjonale-prover/. Accessed November 12, 2021.
2. Eurostat. Statistics Explained. Income to needs ratio. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Glossary:Equivalised_disposable_income. Accessed November 11, 2021.
3. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med.* 2014;275(6):570-580.
4. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health.* 2006;60(7):578-586.
5. Engen TH. Nedenes skole. Nasjonale prøver i engelsk 5.trinn 2011. https://www.nedenes.skole.arendal.no/index.php?artID=344. Accessed November 10, 2021.