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In utero opioid exposure and risk of infections in childhood: A multinational Nordic cohort study

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Abstract

Purpose: There is an increasing number of children with in utero exposure to opioids. Knowledge about opioid safety in pregnancy, particularly for outcomes later in childhood is scarce. It has been suggested that opioids can modulate immune system and increase the risk of infections. Our goal was to study the impact of in utero opioid exposure on the immune system and the risk of infections in childhood.

Methods: This population-based cohort study used nationwide registers from Denmark, Norway, and Sweden. Among pregnant women we identified users of opioids for two different indications, opioids used in opioid maintenance therapy (OMT) and opioids used for treatment of pain. We followed the exposed children and studied susceptibility for infections measured as number of antibiotic prescriptions expressed as Incidence rate ratios (IRRs) and diagnoses in specialist health care expressed as hazard ratios (HRs).

Results: After adjustment we did not observe increased risk for filling antibiotic prescriptions in children exposed to OMT opioids compared with OMT discontinuers (IRR, 1.08; 95% CI 0.81-1.44 in Norway and Sweden, and IRR, 0.74; 95% CI 0.63-0.88 in Denmark), or for diagnosis of infection in specialist health care (HR 0.83; 95% CI 0.55-1.26 in Norway and Sweden, and 0.82; 95% CI 0.62-1.10 in Denmark).

Conclusions: In this population-based cohort study, we did not observe increased risk of infections among children prenatally exposed to OMT opioids when compared to OMT discontinuers, nor long-term analgesic opioids exposed when compared to short-term analgesic opioids exposed.

KEYWORDS
infections, opioids, pharmacoepidemiology, prenatal

1 | INTRODUCTION

Opioids are primarily used for treatment of pain. In addition, certain opioids (methadone mixture and high-dose buprenorphine) are used in treatment of opioid use disorder (OUD) as a part of opioid maintenance therapy (OMT). Several countries have reported dramatic increases in the use of prescription opioids in recent years, a trend that also affected women of child-bearing age.[1-4] Knowledge on the safety of in utero

opioid exposure is incomplete, and studies are needed to understand the effect of opioids on the health of the unborn child.

Opioids cross the placenta and bind to opioid receptors that are present in multiple organs in the developing fetus; as a result, prenatal opioid exposure may have both short- and long-term consequences for the child's health.[5] Children prenatally exposed to opioids are at risk of developing neonatal abstinence syndrome (NAS) at birth, depending on the dose and timing of exposure, and presence of additional risk factors [6,7]. In addition to NAS, children prenatally exposed to buprenorphine and methadone as part of OMT are at higher risk of being born preterm, have lower birth-weight, and smaller head circumference than unexposed children.[8-10] Little is known about the consequences of in utero exposure to any opioids beyond the neonatal period. Although some studies have examined neurodevelopmental outcomes,[11-13] somatic illnesses, including immune function, have so far received little attention.

Opioid-induced modulation of the immune system has been discussed for decades.[14-17] in vitro experiments and animal models showed that specific opioids affect immune function differently depending on their molecular structure, dosage, and duration of exposure.[14-17] Some epidemiological studies have found an association between opioid use and increased risk of infections in nonpregnant patient with existing diagnoses of rheumatoid arthritis and surgically treated cancer.[18-21]

The development and maturation of the immune system begins in early fetal life and continues through infancy and early childhood.[22-24] It is plausible, given their immunomodulatory function, that opioids can alter generation, function, and maturation of the immune cells in the developing fetus. Alterations in neonatal immune system is associated with increased risk for infections and certain chronic diseases, such as asthma and allergy[24,25]. Still, information about the effect of opioids on the developing immune system is scarce. There are only few descriptive studies that have reported increased risk of hospitalization for infections among children born with NAS, and increased risk of infections among children prenatally exposed to methadone and buprenorphine when compared to the general population [26,27].

The aim of this study was to examine the association between prenatal exposure to opioids and risk of infections in childhood. As confounding by indication may be a key concern, we investigated the association within two distinct populations of pregnant women with two different indications: First, in a cohort of women with a history of OMT exposure, we compared OMT exposed with OMT discontinuers preconception. Second, in a cohort of women with analgesic opioid use during pregnancy, we compared long-term users with short-term users. We followed the corresponding cohorts of live born infants into childhood.

KEY POINTS

- Scandinavian countries have nationwide registers with high quality data that offers an opportunity to study exposures during pregnancy and long-term outcomes in children.
- In this article, data from two countries (Norway and Sweden) were pooled prior to analysis to study effects of rare exposures.
- The association was investigated within two distinct populations of pregnant women exposed to the same class of drugs (opioids) but with two different indications.
- The risk for infections in infants was measured as number of antibiotic prescriptions and diagnosis in specialist health care after prenatal opioid exposure.
- In utero opioid exposure does not increase risk of infections in childhood and should not be of concern for pregnant women treated with analgesic or OMT opioids.

2 | METHODS

2.1 | Data source and study population

This study used data from national health registers in Norway, Sweden, and Denmark. Reporting to the health registers is mandatory in all three countries and regulated by national laws. Inhabitants are registered in national health registers with unique Civil Personal Registration number (CPR), which makes it possible to link the information from registers for every individual.[28] For the purpose of this study, health registers in each of the countries were linked: the medical birth register, the prescription register, the patient register and the cause of death register. Further information on the registers is provided in Appendix S1.

Denmark had legal restrictions on data sharing between partner countries. Therefore, we analyzed data separately for (a) women and their infants born in Norway from January 2005 to December 2015 and in Sweden from July 2006 to December 2013, and (b) women and their infants born in Denmark from January 1997 to December 2015.

2.2 | Definition of exposure and comparison groups

We defined OMT drugs as methadone oral solution (ATC-code N07BC02) or high-dose buprenorphine tablets (≥ 2 mg sublingual tablets, ATC-codes N07BC01 or N07BC51) which are almost solely prescribed for the treatment of OUD, and analgesic opioids as drugs with ATC-code N02A (list of ATC-codes and generic name in Table S1). We used number of defined daily doses (DDDs) to characterize duration of exposure to analgesic opioids. To be included in the study, prescription data for each woman should be available for at least 3 months before pregnancy start.

Based on prescription data linked to medical birth registers, we created four mutually exclusive groups:

1. Pregnant women who filled at least one prescription for OMT drugs from pregnancy start until delivery—OMT exposed. We

TABLE 1 Baseline characteristics of mothers and newborns stratified by the exposure group. Figures represent number (percentage) unless stated otherwise

	Norway and Sweden				Denmark			
	OMT		Analgesic opioids[a]		OMT		Analgesic opioids[b]	
	OMT exposed[c]	OMT discontinuers	Long-term exposed	Short-term exposed	OMT exposed[d]	OMT discontinuers	Long-term exposed	Short-term exposed
No of pregnant women	522	156	9982	47 251	287	630	1740	9341
Norway	310 (59.4)	83 (53.2)	1831 (18.3)	18 192 (38.5)	na	na	na	na
Sweden	212 (40.6)	73 (46.8)	8151 (81.7)	29 059 (61.5)	na	na	na	na
Year of birth								
1997-2000	na	na	na	na	85 (29.6)	116 (18.4)	185 (10.6)	1570 (16.8)
2001-2004	na	na	na	na	86 (30.0)	172 (27.3)	339 (19.5)	1878 (20.1)
2005-2008	161 (30.8)	28 (18.0)	3256 (32.6)	14 509 (30.7)	51 (17.8)	144 (22.9)	448 (25.7)	2224 (23.8)
2009-2011	182 (34.9)	52 (33.3)	3828 (38.4)	17 834 (37.7)	28 (9.76)	104 (16.5)	366 (21.1)	1614 (17.3)
2012-2015	179 (34.3)	76 (48.7)	2898 (29.0)	14 908 (31.6)	37 (12.9)	94 (14.9)	402 (23.1)	2055 (22.0)
Season of birth								
Spring	238 (45.6)	74 (47.4)	5138 (51.5)	24 632 (52.1)	132 (46.0)	322 (51.5)	897 (51.6)	4487 (48.0)
Sex of the child								
Boy	261 (50.0)	81 (51.9)	5126 (51.4)	24 293 (51.4)	149 (51.9)	329 (52.2)	884 (50.8)	4829 (51.7)
Maternal age (y)								
<35	405 (77.6)	113 (72.4)	6235 (62.5)	31 030 (65.7)	222 (77.4)	453 (71.9)	1216 (69.9)	7328 (78.4)
Primiparous	228 (43.7)	57 (36.5)	3230 (32.4)	18 759 (39.7)	119 (41.5)	251 (39.8)	581 (33.4)	3419 (36.6)
Missing	0	0	0	0	7 (2.44)	15 (2.38)	35 (2.01)	205 (2.19)
Smoking during pregnancy	353 (67.6)	96 (61.5)	2081 (20.9)	6397 (13.5)	198 (69.0)	459 (72.9)	616 (35.4)	2575 (27.6)
Missing	68 (13.0)	19 (12.2)	616 (6.17)	3641 (7.71)	57 (19.9)	53 (8.41)	103 (5.92)	755 (8.08)
Cohabitant/Married	298 (57.09)	88 (56.41)	8596 (86.1)	41 895 (88.7)	40 (13.9)	78 (12.4)	267 (15.3)	1232 (13.2)
Missing	12 (2.30)	5 (3.21)	371 (3.72)	1249 (2.64)	0	0	0	0
Chronic maternal illness								
Asthma	63 (12.1)	20 (12.8)	1453 (14.6)	4665 (9.87)	28 (9.76)	41 (6.51)	146 (8.39)	552 (5.91)
Reoccurring urinary tract infection	57 (10.9)	24 (15.4)	1760 (17.1)	6100 (12.9)	na	na	na	na
Hepatitis	30 (5.75)	13 (8.33)	11 (0.11)	33 (0.07)	70 (24.4)	201 (31.9)	< 5	36 (0.39)
Concomittant use of drugs during pregnancy								
Total number of prescriptions, mean (SD)	11.56 (23.1)	8.03 (11.8)	12.8 (17.1)	4.89 (6.76)	11.7 (16.5)	5.22 (10.4)	10.2 (14.5)	4.63 (6.13)
No. of pharmacological subgroups, mean (SD)[e]	3.11 (2.60)	2.67 (2.62)	4.00 (2.96)	2.52 (2.14)	2.84 (2.14)	1.86 (1.85)	3.20 (2.36)	2.32 (1.81)
No. of antibiotic prescriptions, mean (SD)[f]	1.11 (3.71)	0.58 (1.01)	0.92 (1.51)	0.82 (1.28)	0.82 (1.26)	0.77 (1.06)	1.22 (1.76)	1.14 (1.48)
Prescription of nonopioid analgesics	65 (12.5)	16 (10.3)	4730 (47.4)	12 427 (26.3)	48 (16.7)	58 (9.21)	794 (45.6)	2800 (30.0)
Prescription of corticosteroids	7 (1.34)	5 (3.21)	545 (5.46)	1049 (2.22)	6 (2.09)	6 (0.95)	65 (3.74)	180 (1.93)
Prescription of drugs for treatment of COPD	77 (14.8)	14 (8.97)	1517 (15.2)	4192 (8.87)	48 (16.7)	60 (9.52)	184 (10.6)	725 (7.76)
Obstetric characteristics								
Cesarean section	124 (23.8)	44 (28.2)	2987 (29.9)	10 090 (21.4)	96 (33.4)	171 (27.1)	660 (37.9)	2632 (28.2)
Neonatal characteristics								

TABLE 1 (Continued)

	Norway and Sweden				Denmark			
	OMT		Analgesic opioids[a]		OMT		Analgesic opioids[b]	
	OMT exposed[c]	OMT discontinuers	Long-term exposed	Short-term exposed	OMT exposed[d]	OMT discontinuers	Long-term exposed	Short-term exposed
Neonatal abstinence syndrom (NAS)	292 (55.9)	37 (23.7)	92 (0.92)	44 (0.09)	183 (63.8)	100 (15.9)	111 (6.38)	43 (0.46)
Preterm birth	46 (8.81)	17 (10.9)	1102 (11.0)	3816 (8.08)	59 (20.6)	90 (14.3)	260 (14.9)	922 (9.87)
Missing	12 (2.30)	0	30 (0.30)	223 (0.47)	5 (1.74)	15 (2.38)	19 (1.09)	138 (1.48)
Low birth weight	50 (9.58)	16 (10.3)	787 (7.88)	2502 (5.30)	60 (20.9)	< 5	180 (10.3)	677 (7.25)
Missing	0	0	20 (0.20)	69 (0.15)	0	< 5	14 (0.80)	115 (1.23)
SGA	34 (6.51)	14 (8.97)	415 (4.16)	1306 (2.76)	39 (13.6)	51 (8.10)	94 (5.40)	413 (4.42)
Missing	12 (2.30)	0	50 (0.5)	180 (0.38)	5 (1.74)	16 (2.54)	25 (1.44)	168 (1.80)
Malformations	33 (6.32)	7 (4.49)	386 (3.87)	1761 (3.73)	31 (10.8)	46 (7.30)	124 (7.13)	597 (6.39)

Abbreviations: COPD, chronic obstructive pulmonary disease; OMT, opioid maintenance therapy; SGA, small for gestational age.
[a]Among analgesic opioids exposed, the most frequently prescribed opioid was codeine, accounting for 74% of all opioids dispensed during pregnancy. The median cumulative dose among short- and long-term users was 135 mg and 900 of oral morphine equivalents, respectively.
[b]The most frequently prescribed opioid was tramadol, accounting for 42% of all opioids dispensed during pregnancy.
[c]One hundred and sixty-nine were dispensed on average 758 DDDs (18 950 mg) methadone and 349 women received on average 418 DDDs (3344 mg) buprenorphine during pregnancy. Four women filled prescriptions for both methadone and buprenorphine.
[d]Two hundred and fifty-four were dispensed on average 156 DDDs (3900 mg) methadone and 26 women received on average 100 DDDs (800 mg) buprenorphine during pregnancy. Seven women filled prescriptions for both methadone and buprenorphine.
[e]ATC (Anatomical Therapeutic Chemical) level 3.

excluded patients who only got methadone tablets and injections, never methadone mixture or high-dose buprenorphine, since they are most likely patients with chronic, severe pain.

2. Pregnant women with at least one prescription of OMT drugs before but not during pregnancy—OMT discontinuers.
3. Pregnant women who were dispensed 30 or more days of supply for analgesic opioids from pregnancy start until delivery but were not in OMT during study period—long-term analgesic opioids exposed.
4. Pregnant women who were dispensed between 1 and 29 days of supply for analgesic opioids from pregnancy start until delivery but were never in OMT during study period—short-term analgesic opioids exposed.

Within the OMT cohort, we compared continuers with discontinuers, and within the analgesic opioid cohort, we compared long-term with short-term users.

2.3 | Outcomes

The studied outcome was infections in children until maximum 12 years of age and measured as (a) filled antibiotic prescriptions and (b) infection as primary or secondary diagnoses in specialist health care. We collected data on filled antibiotic prescriptions, defined as drugs with ATC—code J01, from prescription registers, and data on diagnoses in specialist health care from patient registers (list of codes in Table S2).

2.4 | Confounders and other covariates

We collected information about potential confounders from prescription registers, birth registers and patient registers, described in details in Appendix S1.

2.5 | Statistical analysis

We summarized and described maternal characteristics for each of the four comparison groups. Crude incidence rates (IRs) of antibiotic prescriptions for each of these four groups were calculated as number of antibiotic prescriptions per 1000 person-years (PY) for all time follow-up, and during the age intervals of 0 to 1 year, 1 to 3 years, and 3 to 6 years to evaluate potential changes in the IR.

We calculated unadjusted and adjusted incidence rate ratios (IRRs) using Poisson regression, which assumes that risk stays constant over time. Participants were censored at emigration (in Norway and Denmark), death, or end of study period whichever occurred first. We also calculated IRR for the age groups of 0 to 1 year, 1 to 3 years, and 3 to 6 years.

The association between exposure and the cumulative risk of infection diagnosis in specialist health care system was analyzed using Cox proportional hazard regression, with attained age as the time scale. Follow-up started at birth and ended at first study outcome, or at censoring as already described for Poisson regression.

We assessed IRRs and HRs for OMT exposed vs OMT discontinuers, and long-term vs short-term analgesic opioids exposed.

We used propensity scores to address imbalances in baseline confounder distributions. In logistic regression models, we estimated the probability of receiving treatment, conditional on a set of confounders specifically identified for the OMT models and the analgesic opioids models. We used standardized probability of treatment weighting (SPTW) approach based on the propensity score to estimate the average effect of opioids among the exposed, and assessed balance of baseline characteristics in the weighted population using the standardized mean difference, with 0.1 as a cut-off for evidence of imbalance. Details of propensity score model fitting, including the standardized mean differences before and after applying the SPTW, are included in Table S3.

Normalized SPT weights were included in adjusted Poisson and Cox regressions. We used clustered robust variance estimators for 95% confidence intervals to account for clustering among mothers with multiple pregnancies.

Statistical analyses were conducted using STATA 14 and SAS 9.4 (SAS Institute Inc., Cary, USA).

Range of sensitivity analysis were conducted and described in Appendix S1.

3 | RESULTS

In total 1 471 406 children born in Norway or in Sweden, and 1 207 989 in Denmark during the observation period were included in the study. The baseline characteristics of women within each of the cohorts, OMT cohort (OMT exposed and OMT discontinuers) and analgesic opioids cohort (long- and short-term exposed), were balanced, with some exceptions. In general, OMT exposed and long-term analgesic opioids exposed women seemed to be burdened with more health problems than women in their comparison groups, as reflected in the total number of prescriptions filled, and the number of drugs from distinct therapeutic/pharmacological areas (Table 1).

In Norway and Sweden, the prevalence of hepatitis (5.8%) and corticosteroid prescriptions (1.3%) was lower among OMT exposed compared with OMT discontinuing women (8.3% and 3.2%, respectively). However, smoking during pregnancy (67.6%) and the prevalence of prescriptions for treatment of COPD (14.8%) was higher among OMT exposed than OMT discontinuers (61.5% and 8.9%, respectively).

Smoking during pregnancy was higher among long-term (20.9%) than among short-term analgesic opioids exposed (13.5%). Also, the use of nonopioid analgesics, corticosteroids and drugs for treatment of chronic obstructive pulmonary disease (COPD) was higher among long-term (47.4%, 5.5%, and 15.2%, respectively) than among short-term analgesic opioids exposed (26.3%, 2.2%, and 8.9%, respectively).

Similar trends were observed in Denmark, except that smoking was more prevalent among OMT discontinuers than OMT exposed (72.9% vs 69.0%).

Information on smoking and marital status was missing for 6-13% and 2-4% of the study population, respectively, and varied between the countries and the exposure groups.

TABLE 2 Incidence rates (IRs) for antibiotic prescriptions dispensed to children of opioid maintenance therapy (OMT) mothers, OMT discontinuers, long- and short-term opioid analgesic exposed any time during follow-up, and stratified by age-group

	Any time during follow-up		0-1 y		1-3 y		3–6 y	
Norway and Sweden	**n**	**IR/1000 pyrs (95% CI)**	**n**	**IR/1000 pyrs (95% CI)**	**n**	**IR/1000 pyrs (95% CI)**	**n**	**IR/1000 pyrs (95% CI)**
OMT exposed	1224	403.8 (381.5-427.1)	124	238.4 (198.3-284.2)	597	619.4 (570.7-671.1)	368	372.2 (335.1-412.2)
OMT discontinuers	288	377.1 (334.8-423.3)	39	250.0 (177.8-341.8)	146	520.5 (439.5-612.1)	76	325.7 (256.6-407.6)
Long-term analgesic opioids exposed	36 229	647.7 (641.0-654.4)	5560	559.1 (544.5-574.0)	17 799	952.8 (938.9-966.9)	10 173	537.5 (527.1-548.0)
Short-term analgesic opioids exposed	146 455	543.4 (540.6-546.2)	21 457	455.5 (449.4-461.6)	70 682	808.1 (802.2-814.1)	41 691	463.5 (459-467.9)
Denmark								
OMT exposed	1678	580.0 (552.6-608.4)	225	784.5 (685.3-894.0)	604	1080.4 (995.9-1170.1)	483	624.6 (570.1-682.8)
OMT discontinuers	3962	669.7 (649.0-690.9)	540	865.1 (793.7-941.3)	1599	1311.0 (1247.5-1376.8)	1003	606.1 (569.1-644.8)
Long-term analgesic opioids exposed	11 479	783.6 (769.3-798.1)	1776	1026.0 (978.9-1074.9)	4625	1388.7 (1349.0-1429.3)	3101	731.8 (706.2-758.0)
Short-term analgesic opioids exposed	59 419	730.8 (724.9-736.7)	9455	1019.2 (998.7-1039.9)	23 480	1312.3 (1295.6-1329.2)	15 594	680.3 (669.6-691.0)

Abbreviations: CI, confidence interval; pyrs, person years.

TABLE 3 Risk for infections according to maternal exposure to opioid maintenance therapy (OMT) versus OMT discontinuers any time during follow-up, and stratified by age-group presented as both Incidence rate ratio (IRR) for child's number of antibiotic prescriptions and Hazard ratio (HR) for child's diagnosis of infection in the specialist health care

		Norway and Sweden			Denmark		
Follow-up time		n	IRR unadjusted (95%CI)	IRR PS adjusted (95%CI)	n	IRR unadjusted (95%CI)	IRR PS adjusted (95%CI)
Any time	OMT discontinuers	135	ref	ref	567	ref	ref
	OMT exposed	451	1.01 (0.78-1.30)	1.08 (0.81–1.44)	226	0.80 (0.69-0.93)	0.74 (0.63-0.88)
0-1 y	OMT discontinuers	135	ref	ref	567	ref	ref
	OMT exposed	451	0.93 (0.55-1.60)	0.92 (0.52-1.61)	226	0.88 (0.70-1.10)	0.75 (0.57-0.98)
1–3 y	OMT discontinuers	135	ref	ref	563	ref	ref
	OMT exposed	450	1.07 (0.78-1.46)	1.15 (0.80-1.65)	226	0.79 (0.66-0.93)	0.72 (0.59-0.88)
3–6 y	OMT discontinuers	104	ref	ref	531	ref	ref
	OMT exposed	385	1.02 (0.68-1.52)	1.10 (0.70-1.71)	208	0.95 (0.76-1.18)	0.82 (0.65-1.05)
			HR unadjusted (95%CI)	HR PS adjusted (95%CI)		HR unadjusted (95%CI)	HR PS adjusted (95%CI)
Any time	OMT discontinuers	132	ref	ref	567	ref	ref
	OMT exposed	397	0.88 (0.61-1.27)	0.83 (0.55–1.26)	226	0.86 (0.68-1.10)	0.82 (0.62-1.10)

Abbreviations: CI, confidence interval; PS, propensity scores.

TABLE 4 Risk for infections according to length of maternal exposure to analgesic opioids any time during follow-up and stratified by age-group presented as both Incidence rate ratio (IRR) for child's number of antibiotic prescriptions and Hazard ratio (HR) for child's diagnosis of infection in the specialist health care

		Norway and Sweden			Denmark		
Follow-up time		n	IRR unadjusted (95%CI)	IRR PS adjusted (95%CI)	n	IRR unadjusted (95%CI)	IRR PS adjusted (95%CI)
Any time	Short-term	43 361	ref	ref	8486	ref	ref
	Long-term	9309	1.17 (1.14-1.21)	1.01 (0.97–1.04)	1619	1.09 (1.02-1.15)	1.06 (1.00-1.12)
0-1 y	Short-term	43 361	ref	ref	8486	ref	ref
	Long-term	9309	1.22 (1.16-1.28)	0.97 (0.91-1.02)	1619	0.99 (0.91-1.07)	0.98 (0.90-1.07)
1–3 y	Short-term	43 210	ref	ref	8429	ref	ref
	Long-term	9274	1.18 (1.14-1.22)	1.02 (0.98-1.06)	1609	1.08 (1.01-1.15)	1.05 (0.98-1.12)
3–6 y	Short-term	35 303	ref	ref	7612	ref	ref
	Long-term	7650	1.15 (1.10-1.21)	1.01 (0.96-1.07)	1448	1.09 (1.00-1.09)	1.10 (1.01-1.20)
			HR unadjusted (95%CI)	HR PS adjusted (95%CI)		HR unadjusted (95%CI)	HR PS adjusted (95%CI)
Any time	Short-term	39 747	ref	ref	8486	ref	ref
	Long-term	8918	1.19 (1.15-1.24)	0.97 (0.93–1.00)	1619	1.01 (0.93-1.09)	0.98 (0.89-1.09)

Note: Short-term (<30 days of supply), long-term (≥30 days of supply) based on total amount of defined daily doses (DDD) dispensed during pregnancy.
Abbreviations: CI, confidence interval; PS, propensity scores.

NAS was most frequently diagnosed among infants of OMT exposed and OMT discontinuers. In Norway and Sweden, NAS prevalence in OMT exposed was lower than in Denmark, 55.9% vs 63.8%, but higher among OMT discontinuers, 23.7% vs 15.9%. Prevalence of NAS was below 1% in both long- and short-term analgesic opioid exposed infants in Norway and Sweden. However, in Denmark, 6.4% of long-term analgesic opioid exposed infants suffered NAS vs 0.5% of short-term exposed (Table 1).

IRs of antibiotic prescriptions varied with age, and in all four exposure groups, children between 1 and 3 years of age had the highest rates, and those below age of 1 had the lowest (Table 2). In the combined cohorts from Norway and Sweden, mean follow-up time for OMT exposed and OMT discontinuers was 5.8 and 4.9 years, and for long- and short-term analgesic exposed it was 5.6 and 5.7 years.

The adjusted IRR for antibiotic prescriptions at any time during follow-up in OMT exposed compared with OMT discontinuers was

1.08 (95% CI, 0.81-1.44) in Norway and Sweden, and 0.74 (95% CI, 0.63-0.88) in Denmark, and was in the same range for all age groups. The adjusted HRs for the risk of diagnosis of infection in specialist health care was 0.83 (95% CI, 0.55-1.26) in Norway and Sweden, and 0.82 (95% CI, 0.62-1.10) in Denmark (Table 3). The Kaplan-Meyer curve for the combined Norwegian and Swedish cohort is presented in Figure S1A.

The adjusted IRR for antibiotic prescriptions at any time during follow-up in long-term users compared with short-term users was 1.01 (0.97-1.04) (95% CI, 0.97-1.04) in Norway and Sweden, and 1.06 (95% CI, 1.00-1.12) in Denmark, and the trend was similar for all age groups. The adjusted HRs for diagnosis of infection was 0.97 (95% CI, 0.93-1.00) in Norway and Sweden, and 0.82 (95% CI, 0.62-1.10) in Denmark (Table 4). The Kaplan-Meyer curve for the combined Norwegian and Swedish cohort is presented in Figure S1B.

Findings from sensitivity analyses conducted to account for missing data, residual confounding, exposure misclassification, alternative outcome definitions, differences in follow-up time, and type of OMT were not substantially different from the main analyses (Table S4).

4 | DISCUSSION

In this population-based cohort study, we did not observe increased risk of infections among children prenatally exposed to OMT opioids when compared to OMT discontinuers, nor long-term analgesic opioids exposed when compared to short-term analgesic opioids exposed. These findings were consistent for all age groups, for different definitions regarding length of exposure, type of opioid dispensed, for infections measured as number of dispensed antibiotics, infections diagnosed in specialist health care, and different data sources.

To our knowledge, this is the first study to address possible long-term consequences of in utero exposure to opioids on risk of infections. Existing literature touching this topic consists of two studies; one reported increased risk for hospitalizations for infections among children who suffered NAS at birth, and the other reported higher rates of admissions with a diagnosis related to infection among children prenatally exposed to opioid agonist naltrexone.[26] In both of these studies, authors have compared exposed children with a very different group of unexposed children from the general population, which is in contrast to our study which compares much more similar groups of children of OMT exposed and OMT discontinuers.

Overall, our study asks a clinically relevant question by framing the study as a hypothetical clinical trial: if women on OMT prior to pregnancy were randomly assigned to continuation during pregnancy vs discontinuation, what would the effect of OMT opioids be on the susceptibility to infections in their children? Because OMT exposed and discontinuers have slightly different baseline characteristics, we used a weighting approach to reduce imbalance of measured confounders. Then, we addressed the same question about the effect of analgesic opioids on the susceptibility to infections in children of women who used opioids during pregnancy for a different indication. More specifically, we compared long-term with short- term analgesic opioids exposed and used a weighting approach to reduce imbalance of measured confounders between these two populations. If we had observed a difference between OMT groups but not between long-term and short-term analgesic opioid exposure, it is likely that the effect should be attributed to residual confounding. The consistency between our two main analyses speaks against a causal link between opioid exposure and an increased susceptibility to infection.

Strengths of the current study include that it is population-based using data from nation-wide health registers strengthening generalizability. Data were prospectively collected and not subject to recall bias. Since confounding by indication might be an important source of bias, we have conducted this study in two populations with different indications and different confounder distributions. We made efforts to account for potential confounders within each of the populations, but some residual confounding by use of illicit drugs in the OMT group, and severity and type of pain in the opioids analgesic group, still cannot be excluded, but most plausible such confounding would tend to move estimates away from the null. Confidence intervals for the risk estimates comparing OMT exposed/OMT discontinuers were wide due to small sample size.

Three potential sources of nondifferential misclassification of exposure in this study are missing information on in-hospital opioid use and nonmedical use of opioids (false negatives), and non-adherence to prescriptions (false-positives). OMT mothers regularly take their maintenance opioids under observation, so nonadherence in the OMT group is less likely; however information on drug treatment during hospitalization, including discontinuation or changes to OMT regimen, is not available in our data. Missing information on in-patient drug use and drug use in outpatient specialist care clinics could potentially lead to misclassification of OMT exposed as OMT discontinuers and bias our risk toward the null. Prevalence of NAS among children of OMT discontinuers was above 20%, so mothers in this group have probably used either OMT or illicit opioids. However, risk estimates did not change when we excluded children with NAS from OMT discontinuers.

Previous studies on birth outcomes following in-utero exposure to prescription drugs have successfully pooled the data from Nordic countries for the purpose of analysis of rare outcomes.[29-32] Although the health care systems in the Nordic countries have many similarities, there are some differences in treatment guidelines, type of data being recorded in the registers, coding systems and validity. Therefore, one cannot rule out the possibility that the exposure and the outcomes are more accurately captured and/or recorded in one country than in the others. If the degree of misclassification of OMT discontinuers is lower in Norway and Sweden than in Denmark, this could be part of an explanation of the differences in effect estimates between the Norwegian/Swedish cohort and the Danish cohort. Specifically, Danish estimates suggest a possible protective effect of OMT continuation in pregnancy vs discontinuation before pregnancy when we were looking at the filled antibiotic prescriptions as an outcome. We do not see similar effect for diagnosed infections as an outcome, and possible explanation is that OMT discontinuers in Denmark continue to use illicit drugs (including opioids) and seek medical care only when children get severe symptoms.

Regarding duration and intensity of exposure, we observed no difference in risk when we compared chronic with acute analgesic opioids use. Furthermore, most of the OMT exposed children were exposed to high doses, throughout gestation, so that lack of association between exposure and the risk of infections can hardly be explained by insufficient intensity of exposure.

Our study does not support the hypothesis that in utero opioid exposure adversely affects the development of the immune system of the unborn child, not even in high doses and throughout the pregnancy. Hence, increased risk for infections in exposed children should not be of concern for pregnant women treated with analgesic or OMT opioids. However, given the increasing number of children with in utero exposure to opioids, and the small and inconsistent body of literature on opioid safety in pregnancy, particularly for outcomes later in childhood, this area warrants an urgent need for research.

ETHICS STATEMENT

Use of data was approved by the Regional Ethical Research Board in Norway (2014/358/REK sør-øst D) and the Regional Ethical Review Board in Stockholm, Sweden (2009/775-31/4, 2016/152-32, and 2017/1159-32), and the Norwegian (16/01326-2/SBO) and the Danish Data Protection Agency (J.nr. 2013-41-1789). The national parliaments have on behalf of their populations given informed consent to be included in the registers. According to Danish legislation, no ethical permission is needed for registry-based research in Denmark. The publication has used data from the Norwegian Patient Register (NPR). Authors are solely responsible for the interpretation and presentation of the data provided.

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CONFLICT OF INTEREST

Sonia Hernandez-Diaz has received research funding to her institution from Eli Lilly, Pfizer, and GSK. She has consulted for Roche and has worked with the North American AED pregnancy registry, which is funded by multiple companies, all unrelated to the topic of this manuscript. Brian T. Bateman was an investigator on grants to his institution from Pfizer, Baxalta, GSK, Pacira, and Eli Lilly. He was a consultant on a postpartum hemorrhage quality improvement project sponsored by a grant from Merck for Mothers. He is a consultant to the Alosa Foundation and to Aetion, Inc., all unrelated to the topic of this manuscript; no financial relationships with any companies that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

Dr Mahic and Dr Handal had full access to all study data in Norway and Sweden and Öztürk and Dr Nørgaard had full access to all study data in Denmark and take responsibility for the integrity of the data and accuracy of the data analysis. Mahic, Handal, Hernandez-Diaz: study concept and design. Mahic, Handal, Hernandez-Diaz, Odsbu, Öztürk, Kieler, Nørgaard, Hjellvik, Skurtveit, Wood: acquisition, analysis, or interpretation of data. Mahic, Handal: drafting of the manuscript. All Authors: critical revision of manuscript for important intellectual content. Mahic, Öztürk: statistical analysis. Handal, Skurtveit, Mahic: obtained funding. Handal, Hernandez-Diaz: study supervision.

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REFERENCES

1. 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.
2. 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.
3. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization - United States, 1999-2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):845-849.
4. Wagemaakers FN, Hollingworth SA, Kreijkamp-Kaspers S, Tee EHL, Leendertse AJ, van Driel ML. Opioid analgesic use in Australia and The Netherlands: a cross-country comparison. *Int J Clin Pharmacol*. 2017;39(4):874-880.
5. Malek A, Mattison DR. Drugs and medicines in pregnancy: the placental disposition of opioids. *Curr Pharm Biotechnol*. 2011;12(5):797-803.
6. 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 (Clin Res Ed)*. 2015;350:h2102.
7. Huybrechts KF, Bateman BT, Desai RJ, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. *BMJ (Clin Res Ed)*. 2017;358:j3326.
8. Nechanska B, Mravcik V, Skurtveit S, et al. Neonatal outcomes after fetal exposure to methadone and buprenorphine: national registry studies from The Czech Republic and Norway. *Addiction (Abingdon, England)*. 2018;113(7):1286-1294.
9. Norgaard M, Nielsson MS, Heide-Jorgensen U. Birth and neonatal outcomes following opioid use in pregnancy: a Danish population-based study. *Subst Abuse*. 2015;9(Suppl 2):5-11.
10. Wurst KE, Zedler BK, Joyce AR, Sasinowski M, Murrelle EL. A Swedish population-based study of adverse birth outcomes among pregnant women treated with buprenorphine or methadone: preliminary findings. *Subst Abuse*. 2016;10:89-97.
11. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev*. 2008;84(1):29-35.
12. Konijnenberg C, Sarfi M, Melinder A. Mother-child interaction and cognitive development in children prenatally exposed to methadone or buprenorphine. *Early Hum Dev*. 2016;101:91-97.
13. McGlone L, Mactier H. Infants of opioid-dependent mothers: neurodevelopment at six months. *Early Hum Dev*. 2015;91(1):19-21.

14. Al-Hashimi M, Scott SW, Thompson JP, et al. Opioids and immune modulation: more questions than answers. *Br J Anaesth*. 2013;111(1):80-88.
15. Byrnes EM, Vassoler FM. Modeling prenatal opioid exposure in animals: current findings and future directions. *Front Neuroendocrinol*. 2018;51:1-13.
16. Plein LM, Rittner HL. Opioids and the immune system - friend or foe. *Br J Pharmacol*. 2018;175(14):2717-2725.
17. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. *Am J Ther*. 2004;11(5):354-365.
18. Boland JW, McWilliams K, Ahmedzai SH, Pockley AG. Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review. *Br J Cancer*. 2014;111(5):866-873.
19. Boland JW, Pockley AG. Influence of opioids on immune function in patients with cancer pain: from bench to bedside. *Br J Pharmacol*. 2018;175(14):2726-2736.
20. Wiese AD, Griffin MR, Schaffner W, et al. Long-acting opioid use and the risk of serious infections: a retrospective cohort study. *Clin Infect Dis*. 2018;68(11):1862-1869.
21. Wiese AD, Griffin MR, Stein CM, Mitchel EF Jr, Grijalva CG. Opioid analgesics and the risk of serious infections among patients with rheumatoid arthritis: a self-controlled case series study. *Arthritis Rheumatol*. 2016;68(2):323-331.
22. Restori KH, Srinivasa BT, Ward BJ, Fixman ED. Neonatal immunity, respiratory virus infections, and the development of asthma. *Front Immunol*. 2018;9:1249.
23. Ygberg S, Nilsson A. The developing immune system—from foetus to toddler. *Acta Paediatrica (Oslo, Norway: 1992)*. 2012;101(2):120-127.
24. Zhang X, Zhivaki D, Lo-Man R. Unique aspects of the perinatal immune system. *Nat Rev Immunol*. 2017;17(8):495-507.
25. Reynolds LA, Finlay BB. Early life factors that affect allergy development. *Nat Rev Immunol*. 2017;17(8):518-528.
26. Kelty E, Hulse G. A retrospective cohort study of the health of children prenatally exposed to methadone, buprenorphine or naltrexone compared with non-exposed control children. *Am J Addict*. 2017;26(8):845-851.
27. Uebel H, Wright IM, Burns L, et al. Reasons for Rehospitalization in children who had neonatal abstinence syndrome. *Pediatrics*. 2015;136(4):e811-e820.
28. Furu K, Wettermark B, Andersen M, et al. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic ClinPharmacol Toxicol*. 2010;106(2):86-94.
29. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ (Clinical Research Ed)*. 2015;350:h1798.
30. Kieler H. The Nordic health registers–an important source when evaluating the safety of antidepressants during pregnancy. *Clin Epidemiol*. 2010;2:205.
31. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ (Clinical Research Ed)*. 2012;344:d8012.
32. Selmer R, Haglund B, Furu K, et al. Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy. *Pharmacoepidemiol Drug Saf*. 2016;25(10):1160-1169.

SUPPORTING INFORMATION

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

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