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Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review

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Abstract

CONTEXT—Opioid use and abuse have increased dramatically in recent years, particularly among women.

OBJECTIVES—We conducted a systematic review to evaluate the association between prenatal opioid use and congenital malformations.

DATA SOURCES—We searched Medline and Embase for studies published from 1946 to 2016 and reviewed reference lists to identify additional relevant studies.

STUDY SELECTION—We included studies that were full-text journal articles and reported the results of original epidemiologic research on prenatal opioid exposure and congenital malformations. We assessed study eligibility in multiple phases using a standardized, duplicate review process.

DATA EXTRACTION—Data on study characteristics, opioid exposure, timing of exposure during pregnancy, congenital malformations (collectively or as individual subtypes), length of follow-up, and main findings were extracted from eligible studies.

RESULTS—Of the 68 studies that met our inclusion criteria, 46 had an unexposed comparison group; of those, 30 performed statistical tests to measure associations between maternal opioid use during pregnancy and congenital malformations. Seventeen of these (10 of 12 case-control and 7

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of 18 cohort studies) documented statistically significant positive associations. Among the case-control studies, associations with oral clefts and ventricular septal defects/atrial septal defects were the most frequently reported specific malformations. Among the cohort studies, clubfoot was the most frequently reported specific malformation.

LIMITATIONS—Variabilities in study design, poor study quality, and weaknesses with outcome and exposure measurement.

CONCLUSIONS—Uncertainty remains regarding the teratogenicity of opioids; a careful assessment of risks and benefits is warranted when considering opioid treatment for women of reproductive age.

Opioids are powerful substances that bind to opioid receptors in the brain and body and are capable of producing numerous physiologic effects, including reduced perception of pain and euphoria.[1] Some prescription opioids (eg, methadone and buprenorphine) are also used to treat opioid use disorder (OUD). The use, misuse, and abuse of prescription and illicit opioids in the United States have increased dramatically in recent years, particularly among women. Between 1999 and 2010, women experienced a >400% increase in prescription opioid overdose deaths, and for every overdose death, there were 30 more opioid misuse/abuse emergency department visits.[2]

Overprescribing practices appear to be driving the epidemic. In 2012 alone, prescribers wrote an estimated 259 million opioid prescriptions nationwide, which is equivalent to 82.5 opioid prescriptions per 100 persons in the United States.[3] Among insured, reproductive-aged women, on average, more than one-quarter filled a prescription for an opioid medication each year during 2008 to 2012.[4] Rates of illicit opioid use, including heroin abuse and dependence, are also increasing. From 2002 to 2013, the incidence of women reporting past-year abuse or dependence on heroin increased 100%.[5]

Opioid use is high among pregnant women in the United States as well, with an estimated 14% to 22% of women receiving an opioid prescription during pregnancy.[6,7] From 1998 to 2011, the prevalence of opioid abuse or dependence among pregnant women during hospitalizations for delivery increased 127%.[8] The high rates of prescription and illicit opioid use are a significant public health concern, not only for women, but also for their infants. Opioids have the ability to cross placental and blood-brain barriers, thereby posing risks for fetuses and newborns who are exposed to such drugs in utero.[9] Spontaneous abortion, premature rupture of membranes, preeclampsia, abruption placentae, and fetal death are all potential obstetric complications of prenatal opioid exposure.[10] Adverse neonatal outcomes that have been associated with opioid use during pregnancy include preterm birth,[11–19] small for gestational age,[15,19–21] lower birth weight,[10,13,14,18,19,21,22] reduced head circumference,[17,23–25] and sudden infant death.[26–28] Neonatal abstinence syndrome (NAS) is another adverse outcome commonly reported in newborns prenatally exposed to opioids. The incidence of NAS diagnoses increased nearly fivefold in the United States during 2000 to 2012, which suggests an increasing number of opioid-exposed pregnancies.[29] Neurodevelopmental outcomes of prenatally exposed infants are an additional area of concern, because a recent meta-analysis reported significant impairments

in cognitive, psychomotor, and observed behavioral outcomes in infants and preschool-aged children with chronic intrauterine opioid exposure.[30,31]

The potential teratogenic effects of maternal opioid use during pregnancy are also an area of great public health concern. Congenital malformations are serious, often costly medical conditions that can cause lifelong challenges. They are a leading cause of infant death in the United States, accounting for 20% of all deaths during the first year of life.[32] Furthermore, an estimated $2.6 billion was spent in 2004 in total hospital costs for children and adults with congenital malformations, and it is likely that costs have increased since that time.[33] Congenital malformations can occur at any time during pregnancy, but the first trimester is typically the most vulnerable period. Some malformations can be prevented by identifying modifiable risk factors, such as exposure to teratogenic substances, during this critical period. Two recent studies funded by the Centers for Disease Control and Prevention have linked opioid use during early pregnancy to congenital malformations.[34,35] These studies report a twofold increased risk for some congenital heart defects, neural tube defects, and gastroschisis and highlight the need for a review of the entire body of evidence related to this critical, yet less discussed, public health concern.

The objective of this report was to systematically review the available literature on maternal opioid use during pregnancy and congenital malformations.

METHODS

Data Sources

We identified relevant articles by searching electronic databases, using a combination of opioid- and congenital malformation–related Medical Subject Headings search terms and keywords (Supplemental Materials) for human studies published in the English language. We used the Ovid platform (Ovid Technologies, Inc) to conduct literature searches of Medline (1946 to present) and Embase (1988 to 2016, week 7) for publications indexed through February 19, 2016. We combined and deduplicated the results into a single EndNote X7.5 (Thomson Reuters) library. In addition, we reviewed the reference lists of included publications to identify additional relevant studies.

Study Selection

We included publications in this review if they: (1) were full-text journal articles (we excluded abstracts); (2) reported the results of original epidemiologic research (we excluded case reports, case series, editorials without original data, commentaries without original data, review papers, clinical guidelines, small descriptive studies [<100 participants], and duplicate reports); (3) reported on exposure to opioids during pregnancy (we excluded reports based on exposures during labor/delivery only); and (4) reported the presence or absence of congenital malformations (collectively or as individual subtypes) as an outcome. For simplicity, hereafter, we refer to distinct publications as “studies” and note overlapping data (when known) in Table 1.

We assessed study eligibility in 3 phases, title review, abstract review, and full-text review, using standardized, duplicate review by coauthor pairs. If either reviewer specified that the

study should be included during any of the review phases, it was flagged to be included in the next phase of review. If both reviewers independently determined that a study should be excluded, it was excluded without additional review. During the review phases, we excluded any duplicate studies that were missed in the EndNote deduplication process.

To systematically extract data, we identified data items of interest and created an electronic data extraction form. We then pilot tested and revised the extraction form as needed. During the data extraction phase, the studies were divided between 2 reviewers. After independently extracting data from their assigned studies, the reviewers exchanged studies and checked the extracted data for completeness. Discrepancies were resolved through discussion and, when necessary, by consulting additional coauthor reviewers.

Study Quality Assessment

We assessed the quality of observational studies included in this review by using modified versions of the (1) Methodological Evaluation of Observational Research–Observational Studies of Risk Factors of Chronic Diseases criteria for studies with comparison groups and (2) Methodological Evaluation of Observational Research–Observational Studies of Population Incidence or Prevalence of Chronic Diseases criteria for large descriptive studies.[90] We selected these validated quality assessment checklists because of their ability to distinguish between the external and internal validity of study findings.[90] The specific study qualities that we assessed included generalizability, sampling method, sampling frame selection bias, response rate, outcome measurement, exposure measurement, exposure intensity/dose, information bias, differential data collection, differential measurement, and confounding. In the absence of established definitions, we defined “gold standard” methods of assessing outcomes and exposures as outcomes measured in a standard, valid, and reliable way and precise and/or accurate assessment of exposures, respectively.

RESULTS

Our searches of the Medline and Embase databases yielded a total of 20114 potentially relevant publications, whose titles and abstracts were reviewed (Fig 1). Duplicates and studies deemed ineligible were excluded, leaving a total of 890 studies to be examined in detail. Of the 890 studies reviewed, 62 met our inclusion criteria. We identified an additional 6 relevant studies by reviewing the reference lists of these eligible studies. We summarize the characteristics of the 68 studies included in this review in Table 1.

Studies With an Unexposed Comparison Group

We included 46 studies with a comparison group unexposed to opioids during pregnancy that investigated associations between prenatal opioid exposure and congenital malformations; 13 were case-control studies and 33 were cohort studies.

Case-Control Studies—The majority (8 of 13) of the included case-control studies were published from 1975 through 1998 (Table 2), before the current opioid epidemic[39,40,69–73,89] Seven opioid exposure[34,35,39,70,71,79,83]; of these, 2 studies also assessed congenital malformations associated with codeine and/or oxycodone exposure.[35,39] Five studies

focused specifically on codeine exposures.[40, 69,72,73,89] Most (7 of 13) studies did not specify the indications for maternal opioid exposure, and one of the included studies did not present risk estimates of congenital malformations in infants exposed to opioids.[79]

Ten case-control studies reported statistically significant positive associations between opioid exposure during pregnancy and congenital malformations.[34,35,39,40,43,69–71,83,89] Studies evaluating opioid exposure in aggregate found that use during early pregnancy was associated with an increased risk of congenital malformations overall,[39] as well as heart malformations overall,[34] inguinal hernia with/without obstruction,[39] ventricular septal defects (VSD)/atrial septal defects,[34,39] oral clefts,[39,70,71] dislocated hip/musculoskeletal defects,[39] spina bifida,[34,35] tetralogy of Fallot,[34] hypoplastic left heart syndrome,[34] right ventricular outflow tract obstruction defects,[34] pulmonary valve stenosis,[34] atrioventricular septal defects,[34] isolated clubfoot,[83] neural tube defects,[35] and other heart and circulatory defects.[39] Bracken and Holford[39] also reported that exposure to opioids for the first time during the second trimester was associated with alimentary tract defects.

Eight case-control studies evaluated exposures to specific types of opioids.[35,39,40,43,69,72,73,89] Of these, 4 studies found codeine to be associated with an increased risk of: congenital malformations overall,[39] heart malformations overall,[40,69,89] VSD,[89] and double-outlet right ventricle defects.[89] In 2 studies by Shaw et al,[72,73] codeine use in pregnancy was not significantly associated with congenital cardiac malformations or neural tube defects. Bracken[40] initially reported an increased prevalence of heart malformations in codeine-exposed infants compared with unexposed infants; however, when Bracken[40] recomputed the prevalence ratios to include infants with other malformations as the controls, the association was no longer statistically significant. Yazdy et al[35] reported an increased risk of spina bifida with noncodeine opioid exposures. And Daud et al[43] found an increased risk for respiratory malformations associated with prenatal exposure to morphine. However, in a study that evaluated first-trimester exposure to oxycodone, no increased risk of congenital malformations were reported.[39]

Cohort Studies—The 33 cohort studies with an unexposed comparison group included in our review were published from 1971 through 2015 (Table 3). Similar to the case-control studies, many (17 of 33) of the cohort studies were published before 1999[18,21,24,25,41,45,47,51,53,56,63,74,76,78,85,86,88] Methadone and heroin were the most common opioid exposures evaluated, with methadone maintenance treatment (MMT) as the most common indication for methadone exposure. Ten studies did not calculate risk estimates of congenital malformations in infants exposed to opioids,[13,24,41,45,51,74,80,81,85,85] and in 5 studies, no congenital malformations were reported in any infant.[25,25,57,78,84] Of the remaining 18 cohort studies that performed statistical tests to measure associations,[12,15–,21,47,52,53,56,63,65,66,76,77,87,88] 7 reported statistically significant increased risks of congenital malformations as a result of prenatal opioid exposure.[12,15,19,21,52,55,87] Four of the 7 studies assessed associations with opioid exposure in aggregate,[12,19,21,55] reporting a statistically significant increased risk of congenital malformations overall in 3 studies[19,21,55] and clubfoot (pes equinovarus) in 1 study.[12]

Five of the 7 cohort studies that reported statistically significant increased risks evaluated associations between exposure to specific types of opioids and congenital malformations.[12,15,52,55,87] In 2 studies by Källén et al,[12,52] tramadol exposure in early pregnancy was associated with a statistically significant increased risk of clubfoot. Källén and Reis[52] also reported an increased risk of congenital malformations overall, "relatively severe malformations" (authors excluded preauricular appendix, tongue tie, patent ductus arteriosus in preterm infants, single umbilical artery, undescended testicle, unstable hip or hip (sub) luxation, and nevus), heart malformations overall, and isolated cardiac septum malformations with tramadol exposure in early pregnancy, as well as congenital malformations overall, and "relatively severe malformations" with codeine exposure and an increased risk of heart malformations overall with the use of synthetic opioids in early pregnancy. The remaining 3 studies evaluated associations with methadone exposure; all studies reported an increased risk of malformations overall.[15,55,87] Nørgaard et al[55] also reported an increased risk of malformations associated with prenatal exposure to buprenorphine.

Studies With an Exposed Comparison Group

We identified 15 eligible studies with an exposed comparison group, of which 14 were cohort studies[36, 42, 46, 48, 50, 55, 58–61, 67, 68, 75, 82] and 1 was a cross-sectional study (Table 1).[14] Eleven studies compared methadone exposure to other opioid exposures, including methadone detoxification,[36] methadone with additional drugs,[42] illicit opioids, such as heroin,[14,46,67,68] MMT with tricyclic antidepressant exposure,[48] slow-release oral morphine,[60] and buprenorphine (Table 4).[55,60,61,82] Other studies compared polydrug abuse (including opioids) to alcohol abuse alone,[50] uncontrolled opioid abuse to methadone detoxification,[59] opioid maintenance treatment (OMT) alone to OMT with other prescription medications,[58] and heroin exposure to amphetamine exposure.[75] Five studies did not specify which exposure groups the congenital malformations were observed in, making their findings difficult to interpret.[14,42,59,60,67] No congenital malformations were reported in the main opioid-exposed groups in 4 other studies.[35,48,68,75]

Only 3 of the 15 studies with an exposed comparison group performed statistical tests to compare findings between exposure groups, with mixed results.[45,50,58] Fajemirokun-Odudeyi et al[46] did not report significant differences in the percentage of congenital malformations between infants exposed to methadone and those exposed to heroin. Lund et al[58] reported a significantly higher prevalence of major malformations in children exposed to OMT with other prescribed medications compared with those exposed to OMT alone, but the documented *P* value was > .05. Similarly, Iosub et al[50] stated that there was a statistically significant lower percentage of infants with malformations in the polydrug-exposed group (14%) compared with the alcohol-only-exposed infants (33%). However, the documented *P* value was equal to .05.

The remaining 3 studies compared buprenorphine and methadone exposures.[55,61,82] Lacroix et al[55] described similar malformation rates in buprenorphine-exposed and methadone-exposed infants, and the rates among both prenatally exposed groups were reported to be higher than the general French population. Welle-Strand et al[82] compared infants prenatally

exposed to buprenorphine to those prenatally exposed to methadone and reported 2 cases with malformations (spina bifida and gastroschisis) in the buprenorphine group, but no malformations in the methadone group. Meyer et al[61] also reported 2 cases with malformations; 1 infant with an absent hand in the methadone-exposed group and 1 infant with isolated cleft palate in the buprenorphine-exposed group.

Descriptive Studies

We included 7 large studies (≥100 participants) that described prenatal opioid exposure and congenital malformations, but did not include any comparison group (Table 5).[37,38,44,49,54,62,64] Three of the 7 studies described congenital malformations collectively.[37,38,44] Blumenthal et al[38] reported a higher prevalence of congenital malformations in the heroin-exposed group (12.7 per 1000 live births) than among all live births in New York City (10 per 1000 live births). Blinick et al[37] did not observe any congenital malformations among 61 live births prenatally exposed to methadone and/or heroin. Davis and Chappel[44] reported 4 congenital malformations among the 113 live births included in their study, 2 of which were exposed to methadone at conception; however, the authors stated that their findings of teratogenic and toxigenic effects of opioids were inconclusive.

The remaining 4 studies reported on specific malformations observed with prenatal opioid exposure.[49,54,62,64] Of the infants prenatally exposed to methadone and/or heroin described by Harper et al,[49] congenital malformations were observed in 3 (ie, diaphragmatic hernia, bifid thoracic vertebrae, and polydactyly). Kivistö et al[54] observed malformations in 10 out of 102 infants (ie, pulmonary artery stenosis; VSDs; primary vesicoureteral reflux grade III; primary vesicoureteral reflux grade III–IV with hydronephrosis; duplex thumb with left-sided duplex urinary collecting system; palatal cleft with ankyloglossia; Pierre Robin syndrome with undescended testicle; microtia with stenotic external ear canal; tetralogy of Fallot with bilateral inguinal hernias, multiple skeletal anomalies, and thymic aplasia; and mild hypospadias) prenatally exposed to buprenorphine. Of these, 5 infants had a major anomaly with functional or cosmetic significance, which was reported to be slightly higher than what is observed on average in the general population (3.4%). Miles et al[62] reported 2 cases of cleft palate among infants exposed to methadone during pregnancy (either alone or in combination with illicit substances). Lastly, Newman[64] reported malformations in 7 infants exposed to methadone (ie, heart murmurs [not generally considered a congenital malformation], hernia, bilateral foot deformity, imperforate anus, and esophageal defect).

Study Quality

We used 2 validated checklists to assess the quality of the 68 studies included in this review (Supplemental Figures 3-1, 3-2, 4, and 5).[90] We also presented the distribution of the included studies with respect to their bias characteristics (Fig 2). Among the 46 studies with an unexposed comparison group, 76% were not generalizable, 61% had a high risk of bias based on their sampling frame, and 57% did not report response rates. Additionally, less than half of the studies assessed outcomes and exposures using gold standards (48% and 28%, respectively). However, 61% of the studies evaluated associations after adjusting for potential confounders.

Among the 15 studies with an exposed comparison group, 87% were not generalizable, 80% had a high risk of bias based on their sampling frame, and 73% did not report response rates. Approximately half of these studies used gold standard assessments for the outcome and addressed confounding. However, because many of these studies used data collected from opioid treatment facilities, a much larger proportion (67%) of studies used gold standard measurements for exposure assessment than studies with an unexposed comparison group. Among the 7 descriptive studies, none were generalizable, all had a high risk of bias based on their sampling frame, and none reported response rates. Although only 43% of the descriptive studies had a low risk of bias in outcome assessment, 71% used gold standards to assess exposures.

DISCUSSION

We included 68 studies in this systematic review, of which 30 (12 case-control and 18 cohort studies with an unexposed comparison group) performed statistical tests to measure associations between opioid exposure during pregnancy and congenital malformations. Of those 30 studies, 17 demonstrated statistically significant positive associations between prenatal opioid exposure and at least 1 congenital malformation (Supplemental Table 6); 10 were case-control studies and 7 were cohort studies. Among the 10 case-control studies, oral clefts and VSDs/atrial septal defects were the most frequently reported specific malformations (reported in 3 studies each; Supplemental Table 7), followed by spina bifida, which was reported in 2 studies. Four of these studies also reported statistically significant positive associations with codeine exposure, where heart malformations were the most frequently reported (3 of 4) congenital malformations mentioned. Among the 7 cohort studies, 6 reported increased risks of congenital malformations overall with prenatal opioid exposure, and the most frequently reported specific malformation was clubfoot (reported in 2 studies).

We have considerable concerns regarding the quality of the studies included in this review. There were no randomized controlled trials and few high-quality observational studies that evaluated the association between prenatal opioid use and congenital malformations. However, we acknowledge that this is a limitation of most medication-related studies in the pregnancy literature. The majority of the included studies lacked generalizability, failed to report response rates, and were older publications (published before 1999), which is a concern given the dramatic increases in opioid use since 1999.[91] Although most of the case-control studies with an unexposed comparison group used appropriate sampling frames and methods, almost all of the other studies had flaws in their sampling frame. Many of the studies also had limitations with outcome and/or exposure measurement, which might have resulted in misclassification. Although the studies with an unexposed comparison group would be considered the highest quality of those included in this review, potential information biases were identified in half of them, and confounding was not properly addressed in many. Additionally, over half of the 68 studies included in this review were cohort studies. In general, population-based cohort studies are not ideal for assessing rare outcomes because most have insufficient power to assess specific congenital malformations. Thus, many of the included studies assessed congenital malformations as 1 homogenous, aggregate group. However, congenital malformations are etiologically heterogeneous, and

examining all congenital malformations combined is unlikely to identify potentially teratogenic effects.[92] This underpowering of cohort studies for rare outcomes likely explains why a much higher proportion of the case-control studies (10 of 12) documented statistically significant positive associations between prenatal opioid use and congenital malformations when compared with the cohort studies (7 of 18) included in this review. Furthermore, the majority of the studies included in this review had relatively small numbers of participants, which additionally limits their ability to assess the risk for congenital malformations due to insufficient power.

Limitations and Strengths

It is important to acknowledge some additional limitations of this review. Restricting our literature search to the English language may have led to a lack of heterogeneity among the reported settings and populations. Additionally, restricting to full-text journal articles may have introduced publication bias by excluding any reports of negative findings that did not become full-text publications. Moreover, in instances of substance use, it is rare for only 1 substance to be misused or abused, making it difficult to evaluate and understand the effects of individual substances on birth outcomes.[10] This challenge is compounded by the often absent or insufficient prenatal care observed in pregnant women with OUD, significantly higher rates of tobacco use among pregnant women with substance use disorders,[93] and lifestyle issues associated with illicit drug use that expose pregnant women to sexually transmitted infections and other risks,[94] all of which increase the risk for poor birth outcomes,[94,95] additionally limiting our ability to draw conclusions from study findings. Finally, due to exposure measurement limitations and the overall poor quality of many of the studies included in this systematic review, we were unable to incorporate information on exposure intensity/dose or additionally group the studies by reasons for exposure (eg, illicit, maintenance treatment, or prescribed). Because several factors play a role in substance use among women, including ethnicity, culture, sexual orientation, and socioeconomic status, it is likely that the study populations varied based on the reasons for prenatal opioid exposure[10]; yet, many of the studies we included failed to properly address confounding, which additionally prevents the generalizing of study findings.

Our review has a number of strengths. We attempted to address the potential for retrieval bias that is inherent in most reviews by using well-defined search terms in multiple electronic databases and by hand-searching the reference lists of eligible studies. Another strength was our use of a systematic, standardized, duplicate review process to identify eligible studies and ensure a relatively thorough retrieval of published literature on opioid use during pregnancy and congenital malformations. Finally, we used validated checklists to assess study quality, which allowed for more objective assessments.

CONCLUSIONS

Our findings in this systematic review have implications for future research and clinical practice. Well-designed studies with unexposed comparison groups that estimate measures of association are needed. Ideally, these studies should also have enough power to assess associations between specific opioids used during pregnancy and specific congenital

malformations, rather than malformations and/or opioids as aggregate groups, and to adequately control for potential confounding factors, including polysubstance use and tobacco use. Given the uncertainty that remains regarding the teratogenicity of opioids, a careful evaluation of the potential risks and benefits is warranted when making clinical decisions regarding the use of opioid therapy in reproductive-aged and pregnant women. According to the recent Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain, when opioids are being considered for reproductive-aged women to manage chronic pain, health care providers are encouraged to discuss (1) family planning and (2) how long-term opioid use might affect any future pregnancy.[96] For health care providers caring for pregnant women taking opioid medications, the guidelines recommend that they (1) access appropriate expertise if considering tapering opioids, (2) offer medication-assisted therapy with buprenorphine or methadone to pregnant women with OUD, and (3) arrange for delivery at a facility prepared to monitor, evaluate for, and treat NAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr Lind conceptualized and designed the review, coordinated and supervised the study appraisal phases, screened publications, assessed studies for eligibility, extracted data, and drafted the initial manuscript; Mrs Interrante designed the data collection instruments, led study quality assessments, screened publications, assessed studies for eligibility, extracted data, and reviewed and revised the manuscript; Drs Ailes and Gilboa conceptualized the review, screened publications, assessed studies for eligibility, and reviewed and revised the manuscript; Ms Khan reviewed reference lists for eligible studies and reviewed and revised the manuscript; Drs Honein, Dowling, Razzaghi, Creanga, and Broussard and Ms Frey and Ms Dawson screened publications, assessed studies for eligibility, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Abbreviations

MMT	methadone maintenance treatment
NAS	neonatal abstinence syndrome
OMT	opioid maintenance treatment
OUD	opioid use disorder
VSD	ventricular septal defect

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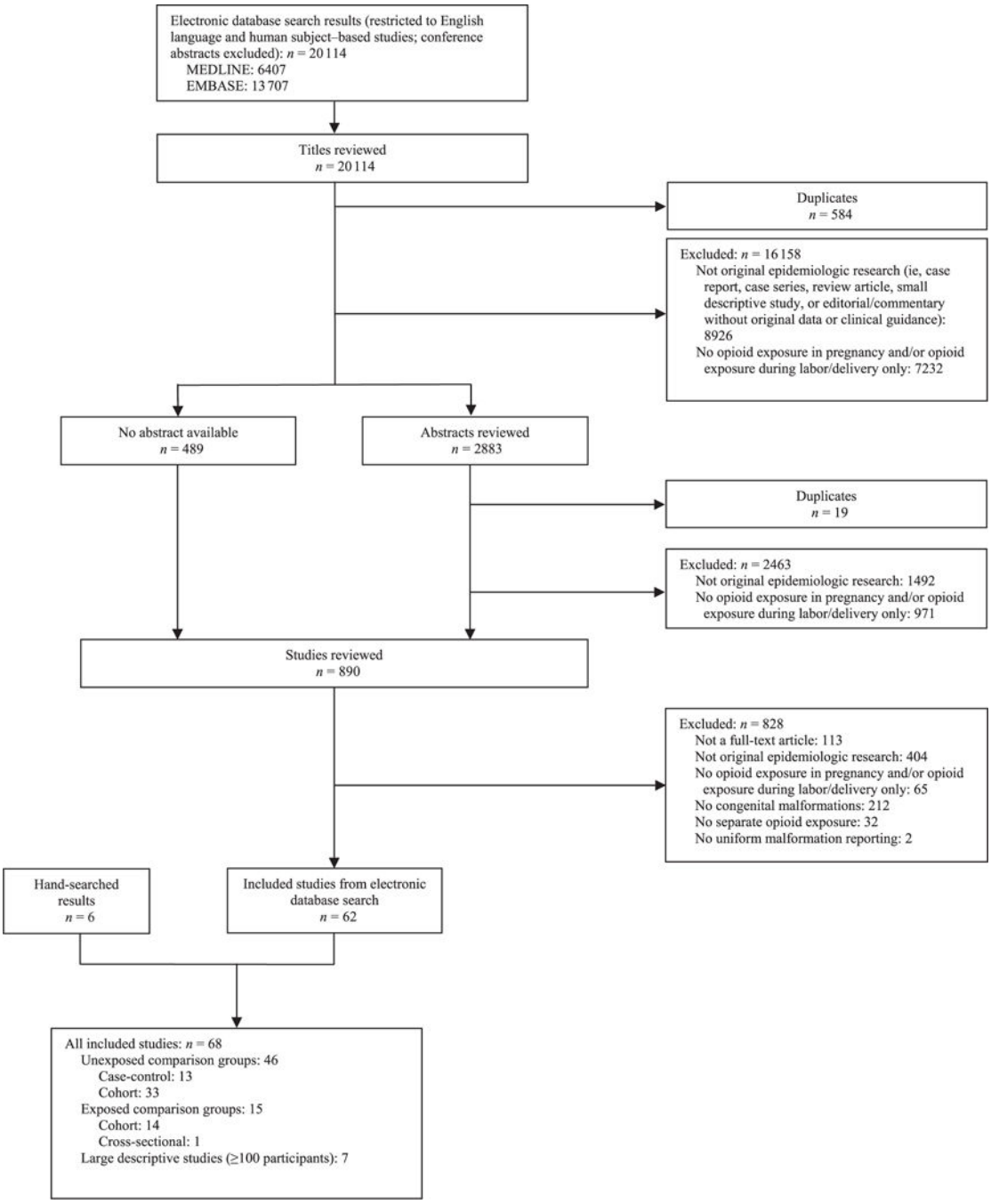

FIGURE 1.

Flowchart for inclusion of studies in a systematic review of prenatal opioid exposure and congenital malformations.

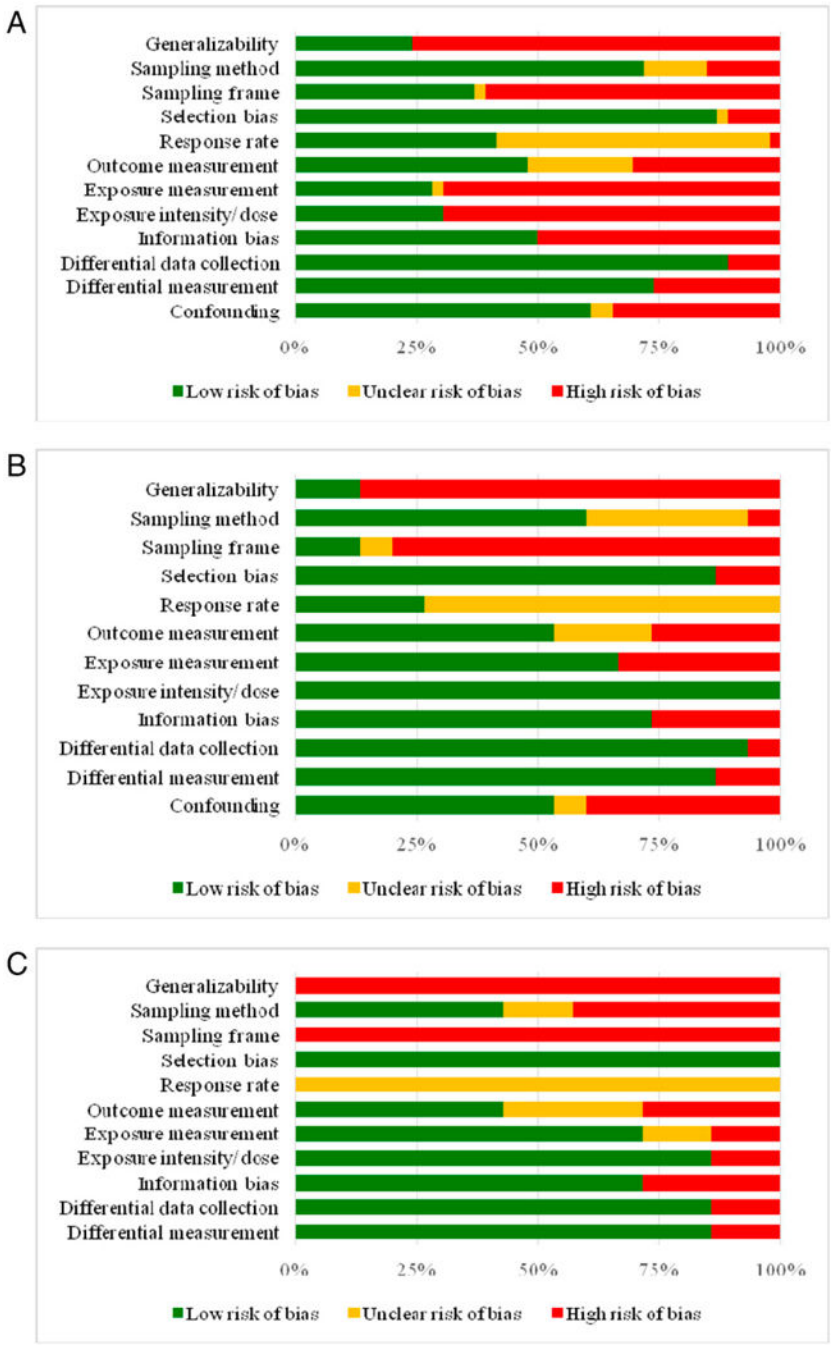

FIGURE 2.

Risk of bias across studies included in a systematic review of prenatal opioid exposure and congenital malformations. (A) Studies with an unexposed comparison group ($n = 46$). (B) Studies with an exposed comparison group ($n = 15$). (C) Descriptive studies ($n = 7$).

TABLE 1

Characteristics of Studies Included in a Systematic Review of Prenatal Opioid Exposure and Congenital Malformations ($n = 68$)

Source	Study Period	Study Type	Country	Population	
				Pregnancies	Infants
Blinick[36] (1971)	NS	Cohort	United States	MMT = 188; methadone detoxification = 211	MMT = 20
Blinick et al[37] (1973)	NS	Descriptive	United States	105	61
Blumenthal et al[38] (1973)	1966–1967 and 1970–1971	Descriptive	United States		By study year 1966 = 153 334 (227 heroin-exposed) 1967 = NS (191 heroin-exposed) 1970 = NS (478 heroin-exposed) 1971 = 131 920 (706 heroin-exposed)
Bracken and Holford[39] (1981)[a]	1974–1976	Case-control	United States		Cases = 1427 Controls = 3001
Bracken[40] (1986)[a]	1974–1976	Case-control	United States		Cases = 330 Controls = 3002
Broussard et al[34] (2011)[b]	1997–2005	Case-control	United States		Cases = 17 449 Controls = 6701
Brown et al[24] (1998)	1993–1996	Cohort	United States	Exposed (methadone) = 32 Exposed (cocaine) = 32 Unexposed (drug-free controls) = 32	
Chasnoff et al[41] (1982)	1976–1980	Cohort	United States		Exposed (conceived on heroin; switched to low-dose methadone) = 39 Exposed (polydrug-abusing mothers) = 19 Unexposed (drug-free controls) = 27
Cleary et al[15] (2011)	2000–2007	Cohort	Ireland	Exposed (receiving methadone at delivery) = 618 Unexposed = 60 412	61 030
Cleary et al[42] (2012)	2009–2010	Cohort	Ireland	MMT = 117	Live births = 114 Intrauterine deaths = 2 Delivered elsewhere = 1
Daud et al[43] (2015)	1997–2013	Case-control	Netherlands		Cases = 4634 Controls = 25 126
Davis and Chappel[44] (1973)	1973–NS	Descriptive	United States	Group I (abstinent group/detox treatment) = 14 Group II (regular treatment/ methadone/no interventions) = 40 Group III (intensified psychosocial support/addiction treatment) = 11 Group IV (intensified psychosocial support given by paraprofessionals/ addiction treatment) = 37	Live births = 113

Source	Study Period	Study Type	Country	Population	
				Pregnancies	Infants
				Group V (interagency care/24 h paging service/transportation/addiction treatment) = 38 Group VI (heroin/no treatment) = 15	
Ellwood et al[45] (1987)	1983–1985	Cohort	Australia	Exposed = 174 narcotic abusers (182 pregnancies) Unexposed = 182	Exposed = 183 live births (5 stillbirths) Unexposed = 182
Fajemirok-Odudeyi et al[46] (2006)	1997–2003	Cohort	England	108	Exposed (methadone) = 54 Exposed (heroin alone or in combination with other drugs, including methadone) = 47 Unexposed (drug-free or drug usage unknown) = 9
Saleh Gargari et al[16] (2012)	2004–2009	Cohort	Iran	Exposed (reporting substance abuse) = 439 (293 opioid-exposed) Unexposed = 519	
Gillogley et al[47] (1990)	1987–1988	Cohort	United States	Exposed (positive urine results for cocaine, amphetamines, and opioids) = 299 (19 positive for opioids alone) Control group = 293	
Green et al[48] (1988)	1983–NS	Cohort	United States		Group I (methadone + TCAs) = 17 Group II (MMT) = 18
Greig et al[17] (2012)	2005–2008	Cohort	England	MSP (methadone) group = 44 Non-MSP group = 88	
Harper et al[49] (1974)	1971–1972	Descriptive	United States	104	Live births = 52
Iosub et al[50] (1985)	1974	Cohort	United States		Group I (alcohol only) = 92 Group II (alcohol + narcotics) = 36
Jicket al[51] (1981)	1977–1979	Cohort	United States	6837[c]	
Kahila et al[26] (2007)	2002–2005	Cohort	Finland	Exposed (buprenorphine) = 67 Reference group/general obstetric population deliveries in Finland 2004 = 57 759	
Källén[12] (2013)[d]	1996–2011	Cohort	Sweden	1 552 382	Exposed (early pregnancy) = 7780 Unexposed (early pregnancy) = 1 568 067
Källén and Reis[52] (2015)[d]	1997–2013	Cohort	Sweden	Exposed = 1751 Unexposed = 1 682 846	Exposed = 1776 Unexposed = 1 797 678
Kandall et al[53] (1977)	1971–1974	Cohort	United States		Drug-dependent mothers = 216 Mothers with past histories of drug abuse (but drug-free during current pregnancy) = 33 Control group = 66
Kivistö et al[54] (2015)	2000–2007	Descriptive	Finland		102

Source	Study Period	Study Type	Country	Population	
				Pregnancies	Infants
Lacroix et al[55] (2011)	1998–2006	Cohort	France	Buprenorphine = 90 Methadone = 45	Fetuses = 135 (buprenorphine = 85 live births; methadone = 40 live births)
Lam et al[56] (1992)	1983–1990	Cohort	China		Exposed = 51 Unexposed = 53
Lendoiro et al[57] (2013)	May 2011– July 2011	Cohort	Spain	209[c]	212[c]
Little et al[18] (1990)	1987	Cohort	United States		Exposed (heroin) = 24 Unexposed = 100
Ludlow et al[13] (2004)	1997–2000	Cohort	Australia	Opioid-using group = 91 Amphetamine-using group = 50 HDWA = 25 291	Opioid-using group = 91 Amphetamine-using group = 50 HDWA = 25 677
Lund et al[58] (2013)[e, f]	2004–2010	Cohort	Norway	Singleton pregnancies = 345 703 (OMT = 159)	
Maas et al[59] (1990)	1983–1989	Cohort	Germany		Mothers with uncontrolled opioid abuse until delivery = 17 Mothers in methadone detoxification program = 58
Metz et al[60] (2015)	1994–2009	Cohort	Austria		Buprenorphine = 77 Methadone = 184 SROM = 129
Meyer et al[61] (2015)	2000–2012	Cohort	United States		Buprenorphine = 361 Methadone = 248
Miles et al[62] (2007)	1991–1994 and 1997–2001	Descriptive	England		By study period 1991–1994 = 78 1997–2001 = 98
Naeye et al[63] (1973)	1954–1972	Cohort	United States		Mothers used heroin during pregnancy up to delivery = 82 Mothers used heroin only during early pregnancy = 10 Mothers in MMT program = 3 Control group (live births) = 500 Control group (autopsies on infants of non–drug-addicted mothers with clinical features of hepatitis) = 7 Control group (autopsies) = 1044
Newman[64] (1973)	1970–1972	Descriptive	United States	120	
Nezvalová-Henriksen et al[65] (2011)[e]	1999–2006	Cohort	Norway	Exposed (codeine) = 2666 Unexposed (no opioids) = 65 316	
Nørgaard et al[66] (2015)	1997–2011	Cohort	Denmark	Exposed (buprenorphine) = 167 Exposed (methadone) = 197 Exposed (heroin) = 28 Exposed (combinations) = 165	Exposed (any opioids) = 564

Source	Study Period	Study Type	Country	Population	
				Pregnancies	Infants
				Unexposed (no opioids) = 949 615	
Olofsson et al[14] (1983)	1970–1979	Cross-Sectional	Denmark	79	89
Ostrea and Chavez[21] (1979)	1973–1976	Cohort	United States		Exposed = 830 (69% methadone and heroin, 31% heroin) Unexposed (drug-free, randomly-selected) = 400 Nursery population = 4811
Ramer and Lodge[67] (1975)	1972–1974	Cohort	United States	32	35
Reddy et al[68] (1971)	1967–1970	Cohort	United States	Heroin = 40 MMT = 3; additional methadone maintained from other hospitals = 2	Heroin = 40 MMT = 3; additional methadone maintained from other hospitals = 2
Rosen and Johnson[25] (1982)	1977–NS	Cohort	United States	Exposed (MMT) = 57 Unexposed (drug-free) = 31	Exposed (MMT) = 62 Unexposed (drug-free) = 32
Rothman et al[69] (1979)	1973–1975	Case-control	United States		Cases = 390 Controls = 1254
Saxén[70] (1975)[g]	1967–1971	Case-control	Finland		Cases = 599 Controls (matched) = 590
Saxén[71] (1975)[g]	1967–1971	Case-control	Finland		Cases = 599 Controls (matched) = 590
Shaw et al[72] (1992)	1981–1983	Case-control	United States		Cases = 141 Controls = 176
Shaw et al[73] (1998)	1989–1991	Case-control	United States		Cases = 538 Controls = 539
Stimmel and Adamsons[74] (1976)	1968–1974	Cohort	United States	Exposed (MMT) = 28 Exposed (heroin/methadone) = 57 Unexposed (drug-free) = 30	Exposed (MMT) = 31 Exposed (heroin/methadone) = 57 Unexposed (drug-free) = 30
Thaithumyanon et al[75] (2005)	1997–2002	Cohort	Thailand	Amphetamine = 178 Heroin = 33 (including 5 women who used both drugs)	211
Thornton et al[76] (1990)	1982–1985	Cohort	Ireland	Exposed = 38 (29 mothers) Unexposed = 38	Exposed = 42 Unexposed = 38
Uebel et al[77] (2015)	2000–2011	Cohort	Australia		With NAS = 3842 Without NAS = 1 018 421
van Baar et al[78] (1989)	1983–1985	Cohort	Netherlands	Exposed = 35 Unexposed = 37	Exposed = 35 Unexposed = 37
van Gelder et al[79](2009)[b]	1997–2003	Case-control	United States		Cases = 10 241 Controls = 4967
Vucinovic et al[19] (2008)	1997–2007	Cohort	Croatia	Exposed = 85 Unexposed = 43 096	Exposed = 86 Unexposed = 43 529

Source	Study Period	Study Type	Country	Population	
				Pregnancies	Infants
Walhovd et al[80] (2007)[h]	NS	Cohort	Norway		Exposed (prenatal polysubstance abuse) =14 (10 heroin-exposed) Unexposed = 14
Walhovd et al[81] (2010)[h]	NS	Cohort	Norway		Exposed (prenatal polysubstance exposure without fetal alcohol spectrum disorder) = 14 Unexposed = 14
Welle-Strand et al[82] (2013)[f]	1996–2009	Cohort	Norway	Buprenorphine = 49 Methadone = 90	Buprenorphine = 49 Methadone = 90
Werler et al[83] (2014)	2007–2011	Case-control	United States		Cases = 646 Controls = 2037
White et al[84] (2006)	Normal birth outcomes: 1999–2000 Illicit drugs database: 1994–NS	Cohort	England	Exposed (amphetamine without treatment) = 41 Exposed (amphetamine with treatment) = 47 Exposed (heroin without treatment) = 17 Exposed (heroin with treatment) = 64 Unexposed (drug-free) = 7666	Normal local population births = 7497
Wilson et al[85](1981)[i]	1974–1977	Cohort	United States	Exposed (untreated drug-dependent) = 29 Exposed (methadone-treated) = 39 Unexposed (drug-free) = 57	Exposed (untreated drug-dependent) = 30 Exposed (methadone-treated) = 39 Unexposed (drug-free) = 58
Wilson[86] (1989)[i]	1974–1977	Cohort	United States	Exposed (untreated drug-dependent) = 29 Exposed (methadone-treated) = 39 Unexposed (drug-free) = 57	
Wouldes and Woodward[87] (2010)	1996–1999	Cohort	New Zealand	Exposed = 30 Unexposed = 42	Exposed = 32 Unexposed = 42
Yazdy et al[35] (2013)	1998–2010	Case-control	United States		Cases = 305 Controls (nonmalformed) = 7125 Controls (malformed) = 13 405
Zelson et al[88] (1971)	1960–1969	Cohort	United States		Exposed = 384 Unexposed (hospital population) = 34 886
Zierler and Rothman[89] (1985)	1980–1983	Case-control	United States		Cases = 298 Controls = 738

HDWA, Health Department of Western Australia; MSP, Methadone Substitution Program; NS, not specified; SROM, slow-release oral morphine; TCA, tricyclic antidepressant.

[a] Overlapping data from selected Connecticut hospitals.

[b] Overlapping data from the National Birth Defects Prevention Study.

[c] Number of exposed and/or unexposed unclear.

[d] Overlapping data from the Swedish Medical Birth Register.

[e] Overlapping data from the Medical Birth Registry of Norway.

[f] Overlapping data from the National OMT Program in Norway.

[g] Overlapping data from the Finnish Register of Congenital Malformations.

[h] Overlapping data from a Norwegian longitudinal project on the development of children born to mothers who used illicit drugs during pregnancy.

[i] Overlapping data from a follow-up study at Houston's public maternity hospital (institution name not specified).

TABLE 2

Case-Control Studies With an Unexposed Comparison Group That Investigated Associations Between Prenatal Opioid Exposure and Congenital Malformations (n = 13)

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
Bracken and Holford[39] (1981)	Narcotic analgesics; codeine; thebaine (oxycodone)	Any and specific major congenital malformations	First exposure to narcotic analgesics in first trimester Major congenital malformations: OR, 3.6; 95% CI, 1.8–7.2 Specific malformations (P < .01): cleft lip/palate; VSD + ASD; and other heart and circulatory defects Specific malformations (P < .05): dislocated hip/musculoskeletal defects; inguinal hernia with/without obstruction Specific malformations (P > .05): alimentary tract; CNS anomalies/spina bifida; heart valve defect; polydactyly/syndactyly; down syndrome; hemangioma; pyloric stenosis; skanomalies; talipes; TGV; and other congenital malformations First exposure to specific opioids in first trimester Codeine: P = .004 Thebaine (oxycodone): P = .07
	Reasons: medical (prescribed)		First exposure to narcotic analgesics in second trimester Major congenital malformations: P > .05 Specific malformations (P < .05): alimentary tract Specific malformations (P > .05): CNS anomalies/spina bifida; cleft lip/palate; dislocated hip/musculoskeletal defects; down syndrome; heart valve defect; hemangioma; inguinal hernia with/without obstruction; polydactyly/syndactyly, pyloric stenosis; skanomalies; talipes, TGV; VSD + ASD; other heart and circulatory defects; and other congenital malformations First exposure to narcotic analgesics in third trimester Major congenital malformations: P > .05
Brack[40] (1986)	Codeine Reasons: medical (prescribed)	CHDs	Controls (without any congenital malformations): PR, 2.4; 95% CI, 1.1–5.2 Controls (including infants with other malformations): PR, 1.3; 95% CI, 0.7–3.9
Broussard et al[34] (2011)	Opioid analgesic treatment (ie, codeine; hydrocodone; meperidine; oxycodone; propoxyphene; morphine; tramadol; methadone; hydromorphone; fentanyl; pentazocine)	Specific major congenital malformations	Non-heart defects Anencephaly/craniorachischisis: aOR 1.7; 95% CI 0.84–3.4 Spina bifida: aOR, 2.0; 95% CI, 1.3–3.2 Cleft palate: aOR, 1.3; 95% CI, 0.84–2.0 Cleft lip with cleft palate: aOR, 1.4; 95% CI, 0.96–2.1 Cleft lip without cleft palate: aOR, 0.68; 95% CI, 0.34–1.3 CHDs Any of included CHDs: aOR, 1.4; 95% CI, 1.1–1.7 Anomalous pulmonary venous return: aOR, 0.71; 95% CI, 0.22–2.3 Aortic stenosis: aOR, 1.3; 95% CI, 0.61–2.9 ASD secundum: aOR, 1.3; 95% CI, 0.94–1.9 ASD not otherwise specified: aOR, 2.0; 95% CI, 1.2–3.6 AVSD: aOR, 2.4; 95% CI, 1.2–4.8 Coarctation of aorta: aOR, 0.88; 95% CI, 0.47–1.6

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
	Reasons: medical (not maintenance treatment)		Conotruncal defects: aOR 1.5; 95% CI, 1.0–2.1 d-TGA: aOR, 1.1; 95% CI, 0.56–2.1 HLHS: aOR, 2.4; 95% CI, 1.4–4.1 Laterality defects with CHD: aOR, 1.2; 95% CI, 0.42–3.2 Left ventricular outflow tract obstruction defects: aOR, 1.5; 95% CI, 1.0–2.2 PVS: aOR, 1.7; 95% CI, 1.2–2.6 Right ventricular outflow tract obstruction defects: aOR, 1.6; 95% CI, 1.1–2.3 Septal defects: aOR, 1.2; 95% CI, 0.93–1.6 Single ventricle/complex: aOR, 1.1; 95% CI, 0.42–3.2 Tetralogy of Fallot: aOR, 1.7; 95% CI, 1.1–2.8 VSD conoventricular: aOR, 2.7; 95% CI, 1.1–6.3 VSD perimembranous: aOR, 0.99; 95% CI, 0.65–1.5 VSD + ASD: aOR, 1.7; 95% CI, 1.0–2.9 VSD + PVS: aOR, 1.3; 95% CI, 0.46–3.7
Daud et al[43] (2015)	Morphine Reasons: medical (prescribed)	Specific congenital malformations (ie, CHDs; musculosk; digestive; urinary; oral clefts; genital; CNS; limb; eye, ear, face, neck; respiratory)	Respiratory: OR, 100.9; 95% CI, 10.39–979.94
Rothman et al[69] (1979)	Codeine Reasons: not specified	CHDs	CHDs: PR, 4.1; 90% CI, 1.3–13
Saxén[70] (1975)	Opioids Reasons: not specified	Oral clefts	Matched-pair analysis: RR, 3.42[a] Random-sample study: RR, 3.40[a] Yule's Q coefficient analysis (describes the degree of association between two 2-category variables) Oral clefts crude association: $P < .025$
Saxén[71] (1975)	Opioids (mainly codeine) Reasons: not specified	Specific congenital malformations	Exposure in first trimester Entire study group: $P < .001$ Specific malformations ($P < .01$): cleft palate with no additional defects; cleft lip with or without cleft palate with no additional defects Specific malformations ($P > .05$): cases with additional defects Exposure in second trimester Entire study group: $P > .05$ Specific malformations ($P > .05$): cleft palate with no additional defects; cleft lip with or without cleft palate with no additional defects; cases with additional defects Exposure in third trimester Entire study group: $P > .05$ Specific malformations ($P > .05$): cleft palate with no additional defects; cleft lip with or without cleft palate with no additional defects; cases with additional defects
Shaw et al[72] (1992)	Codeine Reasons: not specified	CHDs	CHDs: OR, 0.70; 95% CI, 0.20–2.4
Shaw et al[73] (1998)	Codeine Reasons: not specified	NTDs	NTDs: OR, 0.89; 95% CI, 0.35–2.24
van Gelder et al[79] (2009)	Opioids (ie, diacetylmorphine/heroin; oxycodone hydrochloride; hydrocodone bitartrate; methadone) Reasons: illicit; medical (not maintenance treatment)	Specific congenital malformations (ie, NTDs; several CHDs; oral clefts; certain gastrointestinal defects)	Too few infants exposed to estimate risks of congenital malformations

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
Werler et al[83] (2014)	Opioids (ie,hydrocodone; codeine; oxycodone; morphine; methadone; buprenorphine; fentanyl; proxyphene; meperidine) Reasons: not specified	Isolated clubfoot	Any length of opioid exposure Isolated cases: aOR, 1.56; 95% CI, 0.92–2.66 Isolated cases among those with first degree clubfoot relatives: aOR, 1.77; 95% CI, 1.03–3.03 ≤ 14 d of opioid exposure: aOR, 1.44; 95% CI, 0.67–3.12 >14 d of opioid exposure: aOR, 1.65; 95% CI, 0.81–−3.35
Yazdy et al[35] (2013)	Opioids (ie, codeine; oxycodone; hydrocodone; morphine; propoxyphene; meperidine; methadone; tramadol; hydromorphone; butorphanol; heroin; fentanyl; buprenorphine; nalbuphine; diphenoxylate); codeine-containing products; non–codeine- containing products Reasons: illicit; medical (not maintenance treatment)	NTDs (ie, anencephaly; encephalocele; spina bifida); spina bifida separately	Controls (without congenital malformations) Any opioids: all NTDs: aOR, 2.2; 95% CI, 1.2–4.2 Any opioids: spina bifida: aOR, 2.5; 95% CI, 1.3–5.0 Codeine-all NTDs: aOR, 2.5; 95% CI, 1.0–6.3 Codeine: spina bifida: aOR, 2.5; 95% CI, 0.9–7.4 Noncodeine: all NTDs: aOR, 2.2; 95% CI, 1.0–4.9 Noncodeine: spina bifida: aOR, 2.8; 95% CI, 1.3–6.3 Controls (with congenital malformations) Any opioids: all NTDs: aOR, 1.9; 95% CI, 1.0–3.4 Any opioids: spina bifida: aOR, 2.2; 95% CI, 1.1–4.1 Codeine: all NTDs: aOR, 2.0; 95% CI, 0.9–4.7 Codeine: spina bifida: aOR, 2.0; 95% CI, 0.7–5.5 Noncodeine: all NTDs: aOR, 1.9; 95% CI, 0.9–4.1 Noncodeine: spina bifida: aOR, 2.5; 95% CI, 1.1–5.4
Zierler and Rothman[89] (1985)	Codeine Reasons: not specified	Any and specific CHDs	Controls (no congenital malformations) Any CHD: cPOR, 2.0; 90% CI 1.1–3.6 Controls (population) Any CHD (exposure from maternal report): cPOR, 1.9; 90% CI, 0.78–4.4 Any CHD (exposure from obstetric record): cPOR, 2.4; 90% CI, 0.55–10.3 VSD: cPOR, 2.5; 90% CI 1.2–5.2 DORV: cPOR, 5.7; 90% CI 1.2–19.7 Controls (other CHDs) VSD: cPOR, 1.5; 90% CI, 0.60–3.9 DORV: cPOR, 3.2; 90% CI, 0.66–11.6 Controls (other congenital malformations) DORV: aPOR, 5.0; 90% CI, 1.2–21.7

aOR: Adjusted odds ratio; aPOR: Adjusted prevalence odds ratio; ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; CHD: Congenital heart defect; CI: Confidence interval; CNS: Central nervous system; cPOR: Crude prevalence odds ratio; DORV: Double-outlet right ventricle; d-TGA: dextro-transposition of the great arteries; HLHS: Hypoplastic left heart syndrome; NTD: Neural tube defect; OR: Odds ratio; PR: Prevalence ratio; PVS: Pulmonary valve stenosis; RR: Riskratio; TGV: Transposition of the great vessels.

[a]Confidence limits and/or *P* values not specified.

TABLE 3

Cohort Studies With an Unexposed Comparison Group That Investigated Associations Between Prenatal Opioid Exposure and Congenital Malformations (n = 33)

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
Brown et al[24] (1998)	Methadone; other opioids Reasons: illicit; maintenance treatment	Major congenital malformations	Methadone group: 9.3% prevalence of congenital malformations Unexposed group: none of the infants had a congenital malformation
Chasnoff et al[41] (1982)	Polydrug abuse (no methadone); heroin to methadone Reasons: illicit; maintenance treatment	Specific congenital malformations	Polydrug-abuse group: 2 infants with hand deformities (exposed to pentazocine and pyribenzamine) Heroin to methadone group: 5 infants with inguinal hernia (2 also had second-degree hypospadias)
Cleary et al[15] (2011)	Methadone Reasons: maintenance treatment	Congenital malformations (major; minor; chromosomal)	Any congenital malformation: aOR, 2.20; 95% CI, 1.54–3.14 Major congenital malformation: aOR, 1.94; 95% CI, 1.10–3.43 Minor congenital malformation: aOR, 2.12; 95% CI, 1.26–3.56 Chromosomal malformation: aOR, 1.48; 95% CI, 0.19–11.4 Unclassified congenital malformation: aOR, 7.26; 95% CI, 2.58–20.4
Ellwood et al[45] (1987)	Heroin; methadone Reasons: illicit; maintenance treatment	Any and specific congenital malformations	Exposed group: 1 infant with anencephaly Unexposed group: 1 infant with severe spina bifida
Saleh Gargari et al[16] (2012)	Opium; heroin; methadone Reasons: illicit	Any and specific congenital malformations (ie, clubfoot; micropenis; macrocephaly; cardiac anomaly; anomalies of limbs; hypospadias; polydactyly)	Opioid-exposed group: there was no statistically significant difference in congenital malformations between exposed and unexposed groups All drugs (not limited to opioids) group: RR, 2.66; 95% CI, 1.16–6.05
Gillogley et al[47] (1990)	Opioids Reasons: illicit	Any congenital malformations	Opiates-only group: none of the infants had a congenital malformation Multichemical (cocaine, amphetamine, and/or opiates) group: 2.9% prevalence of congenital malformations but there was no statistically significant difference in congenital malformations between exposed and unexposed groups
Greig et al[17] (2012)	Heroin; methadone Reasons: illicit; maintenance treatment	Any congenital malformations	There was no statistically significant difference in congenital malformations between exposed and unexposed groups
Jick et al[51] (1981)	Codeine; propoxyphene N; meperidine; propoxyphene hydrochloride and acetaminophen (Darvocet N) Reasons: medical (prescribed)	Any and specific congenital malformations	Terpin hydrate and codeine group: 1 infant with congenital malformations Propoxyphene N group: 1 infant with congenital malformations Meperidine group: 1 infant with congenital malformations Aspirin + phenacetin + caffeine + codeine phosphate (APC with codeine) group: 3 infants with congenital malformations
Kahila et al[26] (2007)	Buprenorphine Reasons: maintenance treatment	Any congenital malformations	Buprenorphine group: none of the infants had a congenital malformation Controls (population): no mention of prevalence of congenital malformations
Källén[12] (2013)	Opioids (ie, morphine; morphine + spasmolytics; hydromorphone; hydromorphone + spasmaolytics; oxycodone; codeine + paracetamol; ketobemidone; ketobemidone +	Any and specific congenital malformations	Any opioids in early pregnancy Any congenital malformations: OR, 1.02; 95% CI, 0.92–1.12 Chromosomal malformations: OR, 0.83; 95% CI, 0.50–1.37

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
	spasmolytica; pethidine; fentanyl; methadone; dextropropoxyphene; dextropropoxyphene + paracetamol/ aspirin; pentazocine; buprenorphine; tramadol; unspecified opioid; naltrexone; buprenorphine; methadone; buprenorphine combination) Reasons: not specified		Relatively severe congenital malformations: OR, 1.03; 95% CI, 0.91–1.15 NTDs: RR, 1.22; 95% CI, 0.36–2.60 Other CNS malformations: RR, 1.40; 95% CI, 0.60–2.76 Orofacial clefts: OR, 0.49; 95% CI, 0.25–0.96 Any cardiovascular malformations: OR, 1.04; 95% CI, 0.85–1.27 Septal cardiac defect: OR, 1.04; 95% CI, 0.82–1.32 Pyloric stenosis: RR, 0.92; 95% CI, 0.34–2.01 Abdominal wall defect: RR, 1.44; 95% CI, 0.30–4.19 Diaphragmatic hernia: RR, 1.36; 95% CI, 0.28–3.99 Hypospadias: OR, 0.97; 95% CI, 0.65–1.44 Major renal malformations: RR, 0.58; 95% CI, 0.12–1.71 Pes equinovarus: OR, 1.68; 95% CI, 1.10–2.55 Poly- or syndactyly: OR, 0.95; 95% CI, 0.58–1.56 Limb reduction defects: RR, 1.73; 95% CI, 0.75–3.41 Craniostenosis: RR, 0.60; 95% CI, 0.12–1.76 Codeine + paracetamol in early pregnancy: there was no statistically significant difference in congenital malformations Dextropropoxyphene in early pregnancy: there was no statistically significant difference in congenital malformations Tramadol in early pregnancy Any tramadol: pes equinovarus: RR, 3.60; 95% CI, 1.72–6.62 Excluding anticonvulsant: pes equinovarus: RR, 3.88; 95% CI, 1.86–7.13 Excluding women with previous miscarriages and/or born outside Sweden: pes equinovarus: RR, 4.17; 95% CI, 1.35–9.72 Any opioids + anticonvulsants in early pregnancy Relatively severe malformations: RR, 1.37; 95% CI, 0.44–3.19 Any opioids + sedative/hypnotics in early pregnancy Relatively severe malformations: OR, 0.75; 95% CI, 0.44–1.29 Any cardiovascular malformations: RR, 0.49; 95% CI, 0.10–1.44 Any opioids + antidepressants in early pregnancy Relatively severe malformations: RR, 1.09; 95% CI, 0.71–1.68 Any cardiovascular malformations: RR, 1.23; 95% CI, 0.53–2.43
Källén and Reis[52] (2015)	Opioids (ie, tramadol; other opioids not used for MMT; codeine + paracetamol/aspirin; other natural opiates (not codeine); dextropropoxyphene ± paracetamol/ aspirin; other synthetic opioids (not tramadol/dextropropoxyphene) Reasons: medical (prescribed)	Any and specific congenital malformations	Tramadol in early pregnancy Any malformations: aOR, 1.30; 95% CI, 1.06–1.69 Relatively severe malformations: aOR, 1.33; 95% CI, 1.05–1.70 Any cardiovascular malformations: aOR, 1.56; 95% CI, 1.04–2.29 Isolated cardiac septum malformation: aRR, 1.78; 95% CI, 1.02–2.90 Pes equinovarus: aRR, 3.63; 95% CI, 1.61–6.89

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
			Hypospadias: aRR, 0.95; 95% CI, 0.31–2.21 Polydactyly: aRR, 1.77; 95% CI, 0.48–4.33 Codeine in early pregnancy Any malformations: aOR, 1.42; 95% CI, 1.19–1.69 Relatively severe malformations: aOR, 1.42; 95% CI, 1.15–1.76 Any cardiovascular malformations: aOR, 1.38; 95% CI, 0.97–1.96 Isolated cardiac septum malformation: aOR, 1.31; 95% CI, 0.80–2.14 Pes equinovarus: aRR, 1.24; 95% CI, 0.34–3.18 Other natural opiates in early pregnancy Any malformations: aOR, 1.20; 95% CI, 0.80–1.81 Relatively severe malformations: aOR, 1.17; 95% CI, 0.71–1.93 Any cardiovascular malformations: aRR, 0.86; 95% CI, 0.23–2.19 Dextropropoxyphene in early pregnancy Any malformations: aOR, 1.07; 95% CI, 0.91–1.26 Relatively severe malformations: aOR, 1.06; 95% CI, 0.87–1.28 Any cardiovascular malformations: aOR, 0.97; 95% CI, 0.68–1.32 Isolated cardiac septum malformation: aOR, 1.01; 95% CI, 0.62–1.66 Pes equinovarus: aRR, 1.68; 95% CI, 0.72–3.30 Other synthetic opioids in early pregnancy Any malformations: aOR, 1.25; 95% CI, 0.75–2.08 Relatively severe malformations: aOR, 1.30; 95% CI, 0.71–2.38 Any cardiovascular malformations: aRR, 2.94; 95% CI, 1.18–6.06 Isolated cardiac septum malformation: aRR, 1.59; 95% CI, 0.52–3.72
Kandall et al[53] (1977)	Heroin; methadone; heroin + methadone Reasons: illicit; maintenance treatment	Any and specific congenital malformations	Heroin group: 1 infant with stigmata of Down syndrome and 1 infant with isolated microcephaly Methadone group: 1 infant with stigmata of Down syndrome Heroin + methadone group: 1 infant with isolated microcephaly Past history of drug abuse (but drug-free during current pregnancy) group: 1 infant with isolated microcephaly Frequencies of “recognizable” malformations across groups were not statistically significantly different
Lam et al[56] (1992)	Heroin; methadone Reasons: illicit; maintenance treatment	Any congenital malformations	There was no statistically significant difference in congenital malformations between exposed and unexposed groups
Lendoiro et al[57] (2013)	Opioids; methadone; fentanyl Reasons: illicit; medical (prescribed)	Any congenital malformations	None of the infants in either the exposed or the unexposed groups had a congenital malformation
Little et al[18] (1990)	Heroin; methadone Reasons: illicit	Any, major, and specific congenital malformations (ie, hip dislocation; natal teeth; polydactyly; skin tag; supernumerary nipple; umbilical hernia; undescended testes; vaginal tag)	There was no statistically significant difference in congenital malformations between exposed and unexposed groups

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
Ludlow et al[13] (2004)	Heroin alone or with other drugs; heroin with methadone; methadone only Reasons: illicit; maintenance treatment	Specific congenital malformations (ie, talipes; cleft palate and low set ears; coarctation of the aorta, laevocardia, and cerebral anomalies; renal anomaly)	Opioid-exposed group: 3 infants with talipes and 1 infant with cleft palate and low-set ears
Naeye et al[63] (1973)	Heroin; methadone Reasons: illicit; maintenance treatment	Specific congenital malformations (ie, cardiac malformations; tracheoesophageal fistula; diaphragmatic hernia; clubfeet)	Any opioid exposure: there was no statistically significant difference in congenital malformations between exposed and unexposed groups in infants who were stillborn/died within the first 72 h after birth Heroin until delivery group: 4% of infants with cardiac malformations, 4% with tracheoesophageal fistula, and 4% with clubfeet Methadone until delivery group: none of the infants had a congenital malformation Heroin during early pregnancy only group: 10% of infants with diaphragmatic hernia Non-drug-addicted group: 8% of infants with cardiac malformations, 1% with tracheoesophageal fistula, 1% with diaphragmatic hernia, and 1% with clubfeet Non-drug-addicted + hepatitis group: 14% of infants had cardiac malformations
Nezvalova-Henriksen et al[65] (201 1)	Codeine (alone or in fixed combination with paracetamol) Reasons: not specified	Any and major congenital malformations	Any exposure in pregnancy Any congenital malformations: aOR, 0.9; 95% CI, 0.8–1.1 Major congenital malformations: aOR, 0.9; 95% CI, 0.7–1.2 Exposure in first trimester Any congenital malformations: aOR, 0.9; 95% CI, 0.7–1.1 Major congenital malformations: aOR, 0.8; 95% CI, 0.5–1.1 Exposure in second trimester Any congenital malformations: aOR, 0.9; 95% CI, 0.7–1.1 Major congenital malformations: aOR, 0.8; 95% CI, 0.6–1.1 Exposure in third trimester Any congenital malformations: aOR, 1.0; 95% CI, 0.7–1.3 Major congenital malformations: aOR, 1.1; 95% CI, 0.8–1.6
Nørgaard et al[66] (2015)	Any opioids; methadone only; buprenorphine only; heroin only; combinations Reasons: illicit; maintenance treatment; medical (prescribed)	Any congenital malformations	Any opioids group: PR, 2.0; 95% CI, 1.5–2.6 Buprenorphine group: PR, 2.0; 95% CI, 1.2–3.2 Methadone group: PR, 2.4; 95% CI, 1.6 -3.7 Heroin group: PR, 0.9; 95% CI, 0.1–57 Combination group: PR, 1.6; 95% CI, 0.9–2.8
Ostrea and Chavez[21] (1979)	Heroin; heroin and methadone Reasons: illicit	Any and specific congenital malformations	Opioid-exposed group 17 infants with minor congenital malformations 20 infants with significant congenital malformations (2 with hydrocephalus, 2 with interrupted aortic arch, 4 with patent ductus arteriosus, 1 with VSD, 1 with malrotation of the intestines, 2 with posterior urethral valves, 1 with multicystic kidney, 3 with hypospadias, 1 with hypoplastic lung, 1 with cleft lip, and 2 with inguinal hernias)

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
			Controls (unexposed) Significant congenital malformations: $P < .01$ Controls (population) Significant congenital malformations: $P < .01$
Rosen and Johnson[25] (1982)	Heroin; methadone; opioids Reasons: illicit; maintenance treatment	Any congenital malformations	None of the infants had a congenital malformation
Stimmel and Adamsons[74] (1976)	Heroin; methadone Reasons: illicit; maintenance treatment	Specific congenital malformations	Opioid exposed group: 1 infant with microcephaly, 1 infant with polydactyly, and 1 infants with hydrocele
Thornton et al[76] (1990)	Heroin; methadone Reasons: illicit; maintenance treatment	Any and specific congenital malformations	Opioid exposed group 1 infant with gastrointestinal atresia and 1 infant with dislocatable hip in a twin breech Incidence: 4.8%; 95% CI, 0.58%-16.16% Controls (unexposed) 1 infant with CHD Incidence: 2.63%; 95% CI, 0.07%-13.81% Controls (population) Incidence: 2.8%
Uebel et al[77] (2015)	Opioids (assumed based on diagnosis of NAS) Reasons: not specified	Any congenital malformations	NAS-diagnosed group: 3 infants admitted to hospital for congenital malformations No-NAS group: 1359 admitted to hospital for congenital malformations NAS versus no-NAS comparison: $P = .35$
van Baar et al[78] (1989)	Methadone with or without heroin and other drugs Reasons: illicit; maintenance treatment	Any congenital malformations	None of the infants had a congenital malformation
Vucinovic et al[19] (2008)	Heroin and/or methadone with or without other drugs Reasons: illicit	Any and specific congenital malformations	Opioid-exposed group Any congenital malformation: RR 4; 95% CI, 1.9–9.2 Specific congenital malformations: 5 infants with CHDs (3 with VSD, 1 with TGV, and 1 with HLHS), 1 with small intestine malrotation, 1 with polydactyly, and 1 with single umbilical artery
Walhovd et al[80] (2007)	Heroin with or without other substance abuse Reasons: illicit	Myelomeningocele	Heroin-exposed group: 1 infant with myelomeningocele
Walhovd et al[81] (2010)	Opioids; heroin Reasons: illicit	Myelomeningocele	Opioid-exposed group: 1 infant with myelomeningocele
White et al[84] (2006)	Heroin with dihydrocodeine; methadone Reasons: illicit; maintenance treatment	Any and specific congenital malformations	None of the infants had a congenital malformation
Wilson et al[85] (1981)	Heroin; methadone Reasons: illicit; maintenance treatment	Specific congenital malformations (ie, hydrocephalus; flexion contractures; cystic fibrosis)	Heroin-exposed group: 1 infant with hydrocephalus Methadone-exposed group: 1 infant with flexion contractures Unexposed group: 1 infant with cystic fibrosis
Wilson[86] (19 89)	Heroin; methadone Reasons: illicit; maintenance treatment	Any and specific congenital malformations	Heroin-exposed group: 1 infant with spastic diplegia and 1 infant with hydrocephalus
Wouldes and Woodward[87] (2010)	Methadone Reasons: maintenance treatment	Any and specific congenital malformations	High-dose methadone group: 1 infant with periventricular leukomalacia, 1 infant with CHD and left vocal palsy, and 1 infant with cleft palate

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
			None versus low-dose versus high-dose methadone comparison: $P = .003$
Zelson et al[88] (1971)	Heroin	Major congenital malformations	Heroin-exposed group: 1 infant with congenital heart lesion, 1 infant with multiple anomalies including a tracheoesophageal fistula, 1 infant with arthrogryposis multiplex, 1 infant with incontinenti pigmenti, and 7 infants developed inguinal hernias in the immediate newborn period
	Reasons: illicit		Unexposed population (hospital): congenital malformations not reported Congenital malformations did not occur with any more frequency as a result of ingestion of heroin and the many other drugs taken than in the general population

aOR, adjusted odds ratio; CHD, congenital heart defect; CI, confidence interval; CNS, central nervous system; HLHS, hypoplastic left heart syndrome; NTD, neural tube defect; OR, odds ratio; RR, risk ratio; TGV, transposition of the great vessels.

TABLE 4

Studies With an Exposed Comparison Group That Investigated Associations Between Different Prenatal Opioid-Related Exposures and Congenital Malformations (n = 15)

Source	Main Comparison Groups/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
Blinick[36] (1971)	Methadone detoxification versus MMT Reasons: detoxification; maintenance treatment	Any congenital malformation	Methadone detoxification group: 2 infants born with congenital malformations MMT group: none of the infants had a congenital malformation
Cleary et al[42] (2012)	Methadone only versus methadone + additional drugs Reasons: maintenance treatment; illicit	Any and specific congenital malformations	Congenital malformations (exposure group not specified): 1 each of trigonocephaly, VSD, and congenital melanocytic naevus
Fajemirokun-Odudeyi et al[46] (2 0 0 6)	Methadone versus heroin Reasons: maintenance treatment; illicit	Any congenital malformation	χ^2 comparison of congenital malformations between groups: not significant
Green et al[48] (1988)	MMT + TCA exposure versus MMT (no TCA exposure) Reasons: maintenance treatment; illicit (other opioids)	Specific congenital malformations (ie, palate deformity)	MMT + TCA exposed group: 1 palate deformity
losub et al[50] (1985)	Alcohol abuser only versus polydrug abusers (alcohol and narcotics) Reasons: illicit	Major congenital malformations	Prevalence of major congenital malformations: alcohol-only group (group I) = 33% compared with polydrug-abuse group (group II) = 14% ($P = .05$; authors considered this to be statistically significant) Prevalence of major congenital malformations (excluding severe microcephaly): group I = 31.5% compared with group II = 14%
Lacroix et al[55] (2011)	Buprenorphine versus methadone Reasons: maintenance treatment	Any and specific congenital malformations	Malformation rates: similar in the 2 groups of pregnant women (note: higher than the general French population) Buprenorphine group: 1 each of tragus appendix; nasal septum deviation plus short neck; laproschisis; facial abnormalities plus microcephaly; and a therapeutic abortion due to malformation of legs, arms, and genitourinary system Methadone group: 1 polymalformation with facial malformations plus short thorax, short legs, and arms plus syndactyly plus micropenis plus multicystic kidneys; and 1 stillbirth due to achondroplasia
Lund et al[58] (2013)	OMT without other prescribed medications versus OMT with other prescribed medications Reasons: maintenance treatment	Major congenital malformations (ie, hydrocephalus, VSD, clubfoot, hypospadias torticollis, muscle macrocephaly, gastroschisis, trisomy 21, pulmonary infundibular stenosis)	Prevalence of major malformations: significantly higher in children whose mothers were comedicated with opioids, benzodiazepines, or z-hypnotics ($P > .05$ according to table footnote)
Maas et al[59] (1990)	Uncontrolled opioid abuse versus methadone detoxification program Reasons: illicit; detoxification	Any and specific congenital malformations	Congenital malformations (exposure group not specified): 1 pyeloureteral stenosis with vesicoureteral reflux and 1 VSD
Metz et al[60] (2015)	Methadone; buprenorphine; SROM; other opioids Reasons: illicit; maintenance treatment	Any congenital malformations	Congenital malformations (exposure group not specified): 2 infants with cleft lip and palate and 1 infant with trisomy 18
Meyer et al[61] (2015)	Methadone; buprenorphine	Any congenital malformations	Methadone group: 1 infant with absent hand

Source	Main Comparison Groups/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
	Reasons: maintenance treatment		Buprenorphine group: 1 infant with isolated cleft palate
Olofsson et al[14] (1983)	Mainly illicit opioids (intravenous heroin and morphine) versus mainly methadone Reasons: illicit; maintenance treatment	Severe congenital malformations; specific congenital malformations	Congenital malformations (exposure group not specified): 1 infant with gastroschisis and 2 infants with intracranial hemorrhage
Ramer and Lodge[67] (1975)	Methadone versus heroin at conception (subanalysis) Reasons: maintenance treatment; illicit	Any congenital malformations	Congenital malformations (exposure group not specified): there were no congenital malformations noted in any infant except for bilateral rudimentary extra digits on 1 infant
Reddy et al[68] (1971)	Methadone versus heroin Reasons: maintenance treatment; illicit	Serious congenital malformations	Serious congenital malformations: none Heroin group: 3 infants developed inguinal hernias
Thaithumyanon et al[75] (2005)	Heroin exposure versus amphetamine exposure Reasons: illicit; not specified (2 heroin users also received methadone)	Any and specific congenital malformations	Heroin group: none of the infants had a congenital malformation Amphetamine group: 5 infants with congenital malformations; 1 each of large nevus flammeus; pigmented nevus; genu recurvatum (vertex presentation infant); down syndrome; and congenital heart disease (hypoplastic right ventricle)
Welle-Strand et al[82] (20 1 3)	Buprenorphine versus methadone Reasons: maintenance treatment	Any and specific congenital malformations	Buprenorphine group: 1 each of spina bifida and gastroschisis Methadone group: none of the infants had a congenital malformation

SROM, slow-release oral morphine; TCA, tricyclic antidepressant.

TABLE 5

Large Descriptive Studies (≥100 Participants) on Prenatal Opioid Exposure and Congenital Malformations *(n* = 7)

Source	Opioid Exposures/Reasons for Opioid Exposure	Congenital Malformations	Main Findings
Blinick et al[37] (1973)	Methadone; heroin Reasons: illicit; maintenance treatment	Any congenital malformation	None of the infants had a congenital malformation
Blumenthal et al[38] (1973)	Heroin Reasons: illicit	Any congenital malformation	Heroin-exposed: the prevalence of congenital malformations was 12.7 per 1000 live births All live births (New York City): the prevalence of congenital malformations was 10 per 1000 live births
Davis and Chappel[44] (1973)	Methadone; heroin Reasons: illicit; maintenance treatment	Any congenital malformation	4 congenital malformations were noted overall; 2 of which were exposed to methadone at conception. The authors noted that the findings are inconclusive in regards to teratogenic and toxigenic effects
Harper et al[49] (1974)	Methadone; heroin Reasons: illicit; maintenance treatment	Any and specific congenital malformations	Congenital malformations (specific exposure not specified): 1 each of diaphragmatic hernia, bifid thoracic vertebrae, and polydactyly
Kivisto et al[54] (2015)	Buprenorphine Reasons: illicit, maintenance treatment	Any and major congenital malformations	Congenital malformations noted: 1 each of pulmonary artery stenosis, VSDs, multiple VSD, primary vesicoureteral reflux grade III, primary vesicoureteral reflux grade III–IV + hydronephrosis, duplex thumb + left-sided duplex urinary collecting system, palatal cleft and ankyloglossia, Pierre Robin syndrome + undescended testicle, microtia + stenotic external ear canal, tetralogy of Fallot + bilateral inguinal hernias + multiple skeletal anomalies + thymic aplasia (additionally 1 boy had mild hypospadias) Major congenital malformations: 5 of the 10 infants noted above had a major anomaly with functional or cosmetic significance Study infants had slightly more major anomalies than newborns on average in the general population (3.4%)
Miles et al[62] (2007)	Methadone only; methadone + illicit substances (ie, cannabis, heroin, benzodiazepines, crack/cocaine, amphetamines, codeine, and dihydrocodeine) Reasons: illicit; maintenance treatment	Any and specific congenital malformations	Congenital malformations (specific exposure not specified): 2 children were diagnosed with cleft palates; there were no cases of microcephaly
Newman[64] (1973)	Methadone Reasons: maintenance treatment	Specific congenital malformations	Congenital malformations noted: 3 infants had heart murmurs[a]; 1 hernia; 1 bilateral foot deformity; 1 imperforate anus; and 1 esophageal malformation There was no predominance of complications in any ethnic or methadone dosage group

[a]Heart murmurs are not generally considered a congenital malformation.