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Methadone, Pierre Robin sequence and other congenital anomalies: case–control study

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ABSTRACT

Objective Methadone is a vital treatment for women with opioid use disorder in pregnancy. Previous reports suggested an association between methadone exposure and Pierre Robin sequence (PRS), a rare craniofacial anomaly. We assessed the association between gestational methadone exposure and PRS.

Design/setting This case-malformed control study used European Surveillance of Congenital Anomalies population-based registries in Ireland, the Netherlands, Italy, Switzerland, Croatia, Malta, Portugal, Germany, Wales, Norway and Spain, 1995–2011.

Patients Cases included PRS based on International Classification of Disease (ICD), Ninth Edition-British Paediatric Association (BPA) code 75.603 or ICD, Tenth Edition-BPA code Q87.08. Malformed controls were all non-PRS anomalies, excluding genetic conditions, among live births, fetal deaths from 20 weeks' gestation and terminations of pregnancy for fetal anomalies. An exploratory analysis assessed the association between methadone exposure and other congenital anomalies (CAs) excluding PRS. Methadone exposure was ascertained from medical records and maternal interview.

Results Among 87 979 CA registrations, there were 127 methadone-exposed pregnancies and 336 PRS cases. There was an association between methadone exposure and PRS (OR adjusted for registry 12.3, 95% CI 5.7 to 26.8). In absolute terms, this association reflects a risk increase from approximately 1–12 cases per 10 000 births. A raised OR was found for cleft palate (adjusted OR 5.0, 95% CI 2.7 to 9.2).

Conclusions These findings suggest that gestational methadone exposure is associated with PRS. The association may be explained by unmeasured confounding factors. The small increased risk of PRS in itself does not alter the risk–benefit balance for gestational methadone use. The association with cleft palate, a more common CA, should be assessed with independent data.

INTRODUCTION

Methadone maintenance treatment (MMT) improves engagement with antenatal care and pregnancy outcomes relative to ongoing heroin use while also leading to better treatment retention than abstinence-oriented approaches.^{1–3} An ongoing overdose epidemic⁴ and substantial increases in maternal opioid use, neonatal abstinence syndrome and associated expenditure⁵ underscore the importance of safe and effective treatments for opioid use disorder (OUD).

Pierre Robin sequence (PRS) is commonly referred to as the triad of micrognathia, glossoptosis and airway obstruction.⁶ Although there is disagreement among clinicians on the definition,⁷ cleft palate is commonly present. The aetiology is unknown, though some cases may have a genetic basis.^{8–9} Three reports describe a potential association between methadone and PRS.^{10–12} An Irish cohort study reported four cases among 618 methadone-exposed babies and eight cases among 60 412 non-exposed.¹⁰ A series of five methadone-exposed PRS cases was previously described.¹¹ A Scottish study noted that 8% of PRS cases were methadone exposed.¹² Two further reports describe PRS in neonates with gestational methadone exposure.^{13–14}

This case-malformed control study tested the hypothesis that first trimester methadone exposure is associated with PRS. An exploratory analysis examined the association with other anomalies.

PATIENTS AND METHODS

European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based registries. The EUROCAT database includes

anonymised records of CA among live births (LBs), fetal deaths (FDs) from 20 weeks' gestational age (GA) and terminations of pregnancy for fetal anomaly (TOPFAs), henceforth described as 'babies'. The dataset includes information on the mother and baby, diagnosis, exposures and family history.¹⁵

Congenital anomalies (CA) include all major structural anomalies (congenital malformations, deformations, disruptions and dysplasias), chromosomal anomalies and genetic syndromes diagnosed prenatally or postnatally. Defined minor anomalies are excluded.¹⁵ One syndrome and up to eight anomalies are coded by WHO International Classification of Disease (ICD) and British Paediatric Association (BPA) codes. These codes are grouped into 89 subgroups for surveillance and research purposes.¹⁵

All registries used prospectively recorded maternity records for ascertaining medication exposure.¹⁶ In addition, four registries used postnatal interviews and one accessed community pharmacy records (table 1).

The EUROCAT database has been used for pharmacovigilance studies since 2007.¹⁷ Babies with genetic syndromes and chromosomal anomalies are excluded from these studies due to known aetiology. Data were extracted from the EUROCAT central database in April 2014. Details on ethics approvals and consent are available.¹⁸

Study design

We conducted a population-based case malformed-control study¹⁹ to test the association between first trimester methadone exposure and PRS. We compared the odds of methadone exposure among babies with PRS with the odds of exposure among babies without PRS. As there is disagreement as to whether a diagnosis of PRS necessarily includes cleft palate⁷ and as PRS may be undiagnosed in some cases of cleft palate, we conducted a post hoc analysis comparing the odds of methadone exposure among babies with cleft palate excluding PRS cases with the odds of exposure in babies with non-cleft palate, non-PRS anomalies. We also conducted an exploratory analysis to test if other non-PRS anomalies were associated with methadone exposure using EUROCAT standard CA subgroups.¹⁶ We excluded all PRS cases and calculated ORs adjusted for registry comparing the odds of methadone exposure for each anomaly subgroup (cases) with the odds of exposure in all remaining anomaly subgroups (malformed controls).

Case and malformed control definition

EUROCAT defines PRS as a sequence of micrognathia leading to tongue displacement and obstruction of palate closure. PRS may occur as part of a genetic syndrome or in isolation.⁶ In 2013, the EUROCAT Coding & Classification Committee recommended that correct coding includes code Q8708, a micrognathia code (K070) and a cleft palate code (Q35), if present.

Cases of PRS were identified using ICD9-BPA code 75 603 or ICD10-BPA code Q8708, with verification by participating registries. Fifteen PRS cases with a monogenic syndrome were excluded due to known aetiology. PRS cases were classified as isolated or multiple by a panel of three medical geneticists, blind to exposures.²⁰ Isolated PRS includes all cases with no other major anomaly¹⁵; multiple includes PRS cases with additional major anomalies including known teratogenic syndromes. All remaining non-PRS malformed babies, excluding those with genetic (monogenic or chromosomal) syndromes, were classified as malformed controls.

Exposure definition

Methadone exposure was identified using the anatomical therapeutic chemical (ATC) codes N07BC02, N07BC05 and N02AC52, or if methadone was in the drug text field. Registries verified that exposure was in the first trimester (1st day of last menstrual period to 12th week of GA). Exposure was classified as 'methadone only' or methadone with coexposures, that is, teratogenic syndromes or medications other than vitamins/minerals (online supplementary table S1). Additional exposure information (eg, recreational drugs, HIV and hepatitis) was available on an ad hoc basis in 'General Comments' and was used to describe the complexity of exposure but not for statistical analysis. Registries with at least one first trimester methadone exposure were included.

Statistical analysis

Crude OR and 95% CIs for methadone exposure versus no exposure for all/isolated PRS cases were calculated as well as OR adjusted for maternal age (reference group 25–29 years) and adjusted for registry. Maternal age and registry were selected a priori as EUROCAT registries contribute different time periods to the study and have different population maternal age structures (which may change over time). Small numbers of exposed cases limited the ability to adjust simultaneously for maternal age and registry. In addition, 'methadone only' exposure versus no exposure was analysed. These analyses were repeated excluding the Dublin registry to avoid any overlap with a previous study.¹⁰ Statistical analyses were conducted using STATA V.12.0. ORs were calculated using the case control command 'cc'. Adjustment for age and registry used the Mantel-Haenszel method. Sensitivity analyses assessed the potential effect of underascertainment of PRS and misclassification of PRS as cleft palate. A Bonferroni correction was applied in the exploratory analysis examining the association between methadone exposure and non-PRS anomalies. The study was reported in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology statement.

RESULTS

Twelve registries in 11 countries, covering a total of 3 978 229 births, participated in this study (table 1), with a total number of 101 873 babies with CA registered between 1995 and 2011. Following exclusion of babies with chromosomal or genetic syndromes, the final study population included 87 979 babies. There were 336 cases of PRS (table 2). The characteristics of PRS cases and malformed controls are outlined in the online supplementary table S2.

There were 127 babies (cases and controls) with methadone exposure, of which three had a teratogenic syndrome (fetal alcohol syndrome, fetal valproate syndrome and congenital cytomegalovirus infection). General comments regarding recreational drug use histories were recorded for 59 methadone-exposed babies (46%): heroin/cocaine/intravenous drug use was recorded for 29 mothers, 4 had heroin exposure recorded up to 1 year pre-pregnancy, 10 were recorded as being former addicts, 14 mothers had hepatitis C/unspecified hepatitis and 2 mothers had alcohol use recorded. Ninety-four per cent of methadone-exposed cases were LB, 2% were FD and 4% were TOPFA. Mean maternal age was 28.4 years for methadone-exposed pregnancies (range 17–41) and 29.6 years for non-methadone exposed (range 13–54) ($p < 0.01$).

Pierre robin sequence

Methadone exposure was significantly associated with all PRS (OR: 15.5 (95% CI 6.1 to 33.3); and isolated PRS (OR: 13.7 (95% CI 4.3 to 33.1)) (table 3). Adjustment for maternal age or registry did not substantially alter the results. Analysis of 'methadone only' exposures gave similar results (OR: 14.2 (95% CI 3.8 to 38.2) and OR adjusted for registry 11.7 (95% CI 4.2 to 32.3)). Exclusion of the Dublin registry did not significantly alter ORs. Table 4

provides details of the methadone-exposed cases.

Exploratory analysis – other CAs

Cleft palate was associated with methadone exposure (OR:5.0 (95% CI 2.7 to 9.2); table 5). The risk of cleft lip was not raised. Of the 12 exposed cleft palate cases, four had an additional diagnosis of micrognathia (online supplementary table S3) suggesting a potential for PRS misclassification in comparison with 8% (178/2165) of all cleft palate cases.

Table 5 gives the distribution of non-genetic anomalies excluding PRS, among the methadone-exposed and non-methadone-exposed and OR adjusted for registry. Only subgroups with at least three exposures are discussed. Raised ORs were found for respiratory anomalies (adjusted OR (aOR): 3.4 (95% CI 1.8 to 6.4)) and orofacial clefts (aOR: 2.5 (95% CI 1.4 to 4.3)). As lung hypoplasia and dysplasia may be related to other anomalies and prematurity, we repeated the respiratory analysis excluding these cases; the adjusted OR remained significant (3.2 (95% CI 1.5 to 6.8)). All the methadone-exposed lung hypoplasia/dysplasia occurred in neonates with a gestation ≤ 33 weeks, compared with 61% of the non-methadone exposed. Urinary anomalies were significantly less commonly associated with methadone exposure (aOR: 0.4 (95% CI 0.2 to 0.9)). A Bonferroni adjusted p value of 0.002 was used as 24 comparisons were carried out. Respiratory, orofacial clefts and cleft palate were still positively associated with methadone exposure at this threshold, whereas the negative association with urinary anomalies disappeared.

DISCUSSION

This population-based case-malformed control study covering almost 4 million births had a novel finding of a strong association between methadone exposure and PRS. These results provide an important confirmation of previous signals.^{10–12} In addition, we found raised ORs for cleft palate (aOR: 5.0 (95% CI 2.7 to 9.2)) and respiratory anomalies excluding PRS (aOR: 3.4 (95% CI 1.8 to 6.4)).

Comparison with other studies

A systematic review assessing CAs and gestational opioid exposure found associations with oral clefts and cardiac septal defects (three studies each) and spina bifida (two studies).²¹ Apart from oral clefts, these associations were not confirmed in our hypothesis-generating exploratory analysis. In an Irish cohort study, an excess of orofacial clefts in the methadone-exposed group (0.5%) compared with the unexposed group (0.1%) was reported.¹⁰ Previous studies have reported an association between opioid exposure generally and cleft palate.^{22–23} Cleft palate has been previously associated with gestational exposure to cocaine, benzodiazepines and smoking.^{24–26}

Strengths and limitations

This population-based study had a range of strengths including: limited potential for non-responder bias, standardised reporting of CA, limited potential for recall bias with prospective exposure ascertainment and the use of malformed controls, minimising the potential for differential exposure ascertainment. Further strengths include the size of the population covered and the inclusion of TOPFA.

These independent data allowed a study with sufficient power to examine previously reported associations^{10–12} between methadone exposure and PRS, considering the rarity of the exposure-outcome combination. EUROCAT registries have previously been validated by examining associations between medications with known teratogenic effects and CA.²⁷

EUROCAT member registries use a standardised methodology and common software program to transmit anonymised individual records of CA; however, bias due to misclassification of outcomes is possible, due to variations in the definition of PRS.²⁸ This may partly explain the variation in prevalence of PRS in EUROCAT registries. While we would expect misclassification to be non-differential in relation to methadone exposure, there was some evidence that cleft palate may have included some misclassified PRS, particularly among the methadone exposed, thus inflating the cleft palate OR and diluting the PRS OR. This should be borne in mind when interpreting other studies with less detailed diagnostic information. There were 363 cases of PRS (including genetic cases) giving a total prevalence of 0.91 per 10 000 births. This is comparable with the prevalence of 1 per 10 000 births cited by Orphanet (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=718) and previous studies (0.71–1.24 per 10 000 LBs).^{29–30}

Associations with urinary anomalies may be a chance finding due to multiple testing. Respiratory anomalies are a heterogeneous group that makes interpretation of our findings of a higher risk difficult.

As EUROCAT registries cover approximately one-quarter of all European births,³¹ it is not possible to record detailed information on all potential confounders, thus limiting the potential to examine the effect of factors other than methadone exposure on the risk of PRS. Data were not available on the extent of maternal smoking, alcohol use, illicit exposures and nutritional status. Heavy maternal smoking, which is very common among methadone users,³² has been associated with cleft palate with PRS.³³

There are fundamental difficulties with research involving illegal exposures, particularly in determining the full range of gestational exposures. Beyond the diverse pharmacological exposures, the various confounding medical and environmental factors preclude any assessment of causality.³⁴

Fetal alcohol syndrome (FAS) was reported in 10% of a US sample of 100 children consecutively diagnosed with PRS.³⁵ A French case series reported three FAS cases among 110 cases of PRS.³⁶ Heavy alcohol consumption was reported in an Irish study of patients with OUD.³⁷ Approximately 28% of women reported 'hazardous, harmful or dependent alcohol use'. Another Irish study reported on alcohol consumption among pregnant women with OUD.³² 'Any use (last 30 days)' was reported by 27.6% of participants.

Underascertainment of methadone exposure is possible, particularly if the mother was purchasing methadone illegally, but it is unlikely that this would differ between cases and controls. The use of case-malformed control designs to study birth defects has the disadvantage that bias towards the null may occur if malformations among the control group were associated with the exposure (teratogen non-specificity bias).³⁸ We mitigated this by including many different CA in the control group and examining any potential association with methadone exposure for each of these in turn.

Implications for research

Further research should address the causality of the association between methadone and PRS. For example, objective determination of alcohol exposure in pregnant women with OUD and examination of the association between alcohol exposure and PRS is merited. The impact of other exposures such as maternal smoking should also be assessed. Although the efficacy of opioid maintenance treatments in pregnancy has been compared,³⁹ there is a lack of clarity on the agent of choice.⁴⁰ All studies examining gestational treatment of OUD should report on CA to improve the level of data available and provide reassurance to women. The cleft palate and respiratory anomalies signals should be tested using independent data.

Implications for practice

Our findings are relevant to women with OUD and clinicians in primary care, addiction, neonatal and obstetric services. Although this study suggests an association, in absolute terms, the risk of PRS following first trimester methadone exposure is minimal, with a risk increase from approximately 1–12 cases per 10 000 exposed pregnancies. However, if the fivefold CP risk were to be confirmed with independent data, this represents a greater absolute risk increase.

Concerns about the potential risk of PRS should be balanced against the substantial, well-described risks of untreated OUD in pregnancy that may lead to severe adverse outcomes. The small risk of PRS should be balanced against the known relapse³ and dramatic mortality risks with abstinence-oriented approaches.⁴¹ These findings should not be used to deprive women with OUD of access to MMT. This information should constitute one element of comprehensive counselling on the benefits and risks of gestational MMT. Women with OUD should be informed that there is an association between methadone use in early pregnancy and the occurrence of PRS. It should be made clear that this association may be explained by exposures other than methadone and that the absolute risk is small.

PRS may be fatal if an airway cannot be established on delivery. Knowledge of this potential, although rare, association may improve care in the neonatal period and make neonatologists aware of potential airway difficulties.

CONCLUSION

This study supports the a priori hypothesis that first trimester exposure to methadone is associated with PRS. We cannot assess causation due to limitations in relation to potential confounding factors. Women with OUD and clinicians should be aware of this association. Counselling should address the fact that the absolute risk is low and that the association may be explained by factors other than methadone exposure.

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What is already known on this topic?

There is limited evidence suggesting that gestational methadone exposure is associated with congenital anomalies, although individual cohort and case–control studies have suggested an association with specific anomaly subtypes.

What this study adds?

This large population-based study found that gestational methadone exposure was associated with Pierre Robin sequence and cleft palate. These associations may be explained by concomitant exposures in pregnant women with opioid use disorder.

Table 1 EUROCAT registries, sources of medication exposure, time period, total birth population covered, total congenital anomaly (CA) registrations and total CA prevalence per 10 000 births

euROCAT registry	sources of medication exposure*	Time period	Total births (n)	Total CA (n)	Total CA prevalence per 10 000 births (95% CI)	number of methadone exposed
Tuscany, Italy	M, I	1995–2011	475 086	10 435	219.64 (215.47 to 223.90)	9
Dublin, Ireland	M	1995–2011	394 585	7908	200.41 (196.04 to 204.88)	23
North Netherlands	M, I, P	1995–2011	323 728	8698	268.68 (263.09 to 274.39)	2
Emilia Romagna, Italy	M, I	1995–2011	555 799	11 368	204.53 (200.81 to 208.33)	8
Vaud, Switzerland	M	1997–2011	112 156	4422	394.27 (382.82 to 406.07)	6
Zagreb, Croatia	M	1995–2011	112 115	1950	173.93 (166.38 to 181.82)	2
Malta	M	1996–2011	67 362	2114	313.83 (300.73 to 327.49)	5
South Portugal	M	1995–2011	307 773	3394	110.28 (106.63 to 114.05)	2
Saxony Anhalt, Germany	M, I	2005–2011	120 931	3766	311.42 (301.63 to 321.52)	7
Wales, UK	M	1998–2011	466 301	18 250	391.38 (385.74 to 397.10)	42
Norway†	M	1999–2011	774 985	23 424	302.25 (298.40 to 306.15)	8
Valencia Region, Spain	M	2007–2011	267 408	6144	229.76 (224.09 to 235.58)	13
Total			3 978 229	101 873	256.08 (254.51 to 257.65)	127

*Sources of medication exposure: prospectively recorded maternity records (M), maternal interview after birth (I) and community prescription records (P).

†Norway total CA registrations and total CA prevalence excludes TOPFA, as no medication exposures recorded in central database for TOPFA.

CA, congenital anomaly; EUROCAT, European Surveillance of Congenital Anomalies; TOPFA, terminations of pregnancy for fetal anomaly.

Table 2 Total number of babies with Pierre Robin sequence and orofacial cleft excluding genetic conditions in 12 EUROCAT registries, 1995–2011

registry	Total Pierre robin (n)	Total orofacial clefts (n)	Total cleft palate (n)	Total Pierre robin with cleft palate diagnosis (n)	Prevalence of Pierre robin per 10 000 births (95%CI)
Tuscany, Italy	11	410	163	8	0.23 (0.13 to 0.42)
Dublin, Ireland	51	523	272	50	1.29 (0.98 to 1.70)
North Netherlands	34	606	193	31	1.05 (0.75 to 1.47)
Emilia Romagna, Italy	43	562	235	31	0.77 (0.57 to 1.04)
Vaud, Switzerland	19	156	75	18	1.69 (1.08 to 2.66)
Zagreb, Croatia	6	147	59	1	0.54 (0.24 to 1.19)
Malta	10	130	78	9	1.48 (0.80 to 2.76)
South Portugal	15	222	93	13	0.49 (0.29 to 0.81)
Saxony Anhalt, Germany	9	210	79	5	0.74 (0.39 to 1.43)
Wales, UK	78	812	376	77	1.67 (1.34 to 2.09)
Norway	32	1342	465	22	0.41 (0.29 to 0.58)
Valencia Region, Spain	28	215	77	13	1.05 (0.72 to 1.52)
Total	336*	5335	2165	278†	0.84 (0.76 to 0.94)

*272 were classified as isolated (81%), and five had teratogenic syndromes (four fetal alcohol syndrome and one fetal valproate syndrome).

†Excludes four PRS cases with cleft lip with/without palate (one in Dublin, one in Vaud and two in Norway).

EUROCAT, European Surveillance of Congenital Anomalies.

Table 3 ORs for PRS associated with methadone exposure

	number of methadone exposures	Crude Or (95% CI)	Or adjusted maternal age (95% CI)	Or adjusted registry (95% CI)
All PRS	7	15.5 (6.1 to 33.3)	16.5 (7.6 to 35.6)	12.3 (5.7 to 26.8)
Isolated PRS	5	13.7 (4.3 to 33.1)	14.5 (5.9 to 35.7)	11.40 (4.6 to 28.3)
All PRS, excluding Dublin*	3	8.6 (1.7 to 26.0)	9.1 (2.8 to 28.8)	7.1 (2.2 to 22.5)

*Dublin registry excluded to avoid overlap with a previous cohort study.
PRS, Pierre Robin sequence.

Table 4 Case list of the seven PRS cases exposed to methadone

	ICD code	Text description*	Classification of Prs	exposures †
1	Q8708 Q3599	Pierre Robin Sequence Cleft palate	Isolated	Methadone only
2	Q3519 K0700 Q8708	Cleft hard palate Micrognathia Pierre Robin Sequence	Isolated	Methadone, diazepam
3	Q8708 Q3559 K071 L059 Q188 P059 Q668*	Pierre Robin sequence Cleft hard palate with cleft soft palate unspecified Retrognathia Sacral dimple Dysmorphic features (forehead and ears) Fetal growth retardation Clubfoot of postural origin – other congenital deformities of feet	Isolated	Methadone only
4	Q8708 Q353 K070	Pierre Robin sequence Cleft of soft palate Micrognathia	Isolated	Methadone only
5	Q355 K070 Q8708 Q435 Q189*	Cleft hard palate with cleft soft palate Micrognathia Likely Pierre Robin sequence Anteriorly placed anus ‡ Soft dysmorphic features (low-set ears, flattened bridge to her nose)	Isolated	Methadone only
6	Q860 Q8708 Q3599 K0700	Foetal alcohol Pierre Robin Sequence Complex cleft secondary palate Micrognathia	Teratogenic syndrome	Methadone, alcohol
7	Q8680 Q353 Q699 K070 Q8708	Sodium valproate embryopathy Cleft soft palate Polydactyly unspecified* Micrognathia Pierre Robin Sequence	Teratogenic syndrome	Methadone, sodium valproate

*Five of the cases were classified as isolated PRS. There were no significant differences in maternal age between methadone-exposed and non-exposed PRS cases (mean 30.6 years). All methadone exposed PRS were aged over 25 years.

†Four cases had 'methadone only' exposure and three had exposure to methadone and other agents (one fetal alcohol syndrome, one valproate and one diazepam).

‡Minor anomalies on the EUROCAT exclusion list.

EUROCAT, European Surveillance of Congenital Anomalies; ICD, International Classification of Disease.

Table 5 Adjusted* ORs for EUROCAT congenital anomaly subgroups†

	non-methadone exposed		methadone exposed		Or _{adj} (95% CI)‡
	n	%	n	%	
All non-genetic anomalies excluding cases of Prs†	87 643	100	120	100	
Nervous system	6820	7.8	7	5.8	0.6 (0.3 to 1.3)
Neural tube defects	2678	3.05	3	2.5	0.7 (0.2 to 2.1)
Anencephalus and similar	930	1.1	1	0.8	—
Spina bifida	1413	1.6	2	1.7	—
Microcephaly	904	1.0	2	1.7	—
Arhinencephaly/holoprosencephaly	235	0.3	1	0.8	—
Eye	2023	2.3	3	2.5	0.9 (0.3 to 2.8)
Congenital cataract	593	0.7	1	0.8	—
Congenital heart defects (CHDs)	28 387	32.4	43	35.8	1.1 (0.8 to 1.7)
Severe CHD	6479	7.4	5	4.2	0.5 (0.2 to 1.2)
Transposition of great vessels	1254	1.4	1	0.8	—
Ventricular septal defect	13 474	15.4	18	15.0	1.0 (0.6 to 1.7)
Atrial septal defect	6415	7.3	12	10.0	1.3 (0.7–2.4)
Tetralogy of Fallot	1012	1.2	2	1.7	—
Pulmonary valve stenosis	1607	1.8	1	0.8	—
Pulmonary valve atresia	380	0.4	1	0.8	—
Coarctation of aorta	1346	1.5	1	0.8	—
Patent ductus arteriosus as only CHD in term infants (gestational age+37 weeks)	1859	2.1	1	0.8	—
Respiratory§	2217	2.5	11	9.2	3.4 (1.8 to 6.4)¶
Choanal atresia	279	0.3	2	1.7	—
Cystic adenomatous malformation of lung	200	0.2	2	1.7	—
Orofacial clefts	5038	5.7	15	12.5	2.5 (1.4 to 4.3)¶
Cleft lip with or without cleft palate	3163	3.6	3	2.5	0.8 (0.2–2.4)
Cleft palate	1875	2.1	12	10.0	5.0 (2.7 to 9.2)¶
Digestive system	6115	7.0	13	10.8	1.5 (0.9 to 2.7)
Duodenal atresia or stenosis	295	0.3	2	1.7	—
Atresia or stenosis of other parts of small intestine	359	0.4	2	1.7	—
Anorectal atresia and stenosis	1008	1.2	2	1.7	—
Hirschsprung's disease	447	0.5	1	0.8	—
Diaphragmatic hernia	936	1.1	2	1.7	—
Abdominal wall defects	1507	1.7	4	3.3	1.7 (0.6 to 4.5)
Gastroschisis	832	0.9	3	2.5	2.2 (0.7 to 6.8)
Omphalocele	574	0.7	1	0.8	—
Urinary	10 478	12.0	7	5.8	0.4 (0.2 to 0.9)**
Congenital hydronephrosis	4418	5.0	5	4.2	0.8 (0.3 to 1.9)
Posterior urethral valve and/or prune belly	347	0.4	1	0.8	—
Genital	8536	9.7	8	6.7	0.7 (0.3 to 1.3)
Hypospadias	7148	8.2	5	4.2	0.5 (0.2 to 1.2)
Limb	20 088	22.9	20	16.7	0.8 (0.5 to 1.2)
Limb reduction	1760	2.0	3	2.5	1.2 (0.4 to 3.8)
Upper limb reduction	1176	1.3	2	1.7	—
Lower limb reduction	626	0.7	2	1.7	—
Clubfoot – talipes equinovarus	4528	5.2	11	9.2	1.7 (0.9 to 3.2)
Clubfoot excluding spina bifida	4399	5.0	11	9.2	1.8 (1.0 to 3.4)
Polydactyly	3229	3.7	2	1.7	—
Syndactyly	1928	2.2	4	3.3	1.7 (0.6 to 4.6)
Craniosynostosis	916	1.0	1	0.8	—
Congenital skin disorders	1522	1.7	4	3.3	2.5 (0.9 to 6.8)

*Adjusted for registry.

†One baby can be counted in more than one subgroup if he or she has multiple anomalies but only once in the total. All PRS cases have been excluded. Only subgroups with methadone exposure are listed.

‡Adjusted ORs are not shown where the number of exposed cases is below three.

§Respiratory subgroup: this heterogeneous subgroup includes four cases of hypoplasia and dysplasia of lung, two cases of choanal atresia, two cases of cystic adenomatous malformation of lung, one case of sequestration of lung, one case with other anomalies of the nose and one case of congenital cystic lung.

¶Statistically significant at $p < 0.001$.**Statistically significant at $p < 0.05$.

GA, gestational age; PRS, Pierre Robin sequence.