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Hospitalization of children after prenatal exposure to opioid maintenance therapy during pregnancy: a national registry study from the Czech Republic

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ABSTRACT

Background and Aims Our understanding of the long-term safety of prenatal exposure to opioid maintenance treatment (OMT) is insufficient. We compared childhood morbidity (0–3 years) between OMT-exposed and relevant comparison groups. **Design** Nation-wide, registry-based cohort study. Registries on reproductive health, addiction treatment, hospitalization and death were linked using identification numbers. **Setting** The Czech Republic (2000–14). **Participants** Children with different prenatal exposure: (i) mother in OMT during pregnancy (OMT; $n = 218$), (ii) mother discontinued OMT before pregnancy (OMT-D; $n = 55$), (iii) mother with opioid use disorder, but not in OMT during pregnancy (OUD; $n = 85$) and (iv) mother in the general population (GP) ($n = 1\,238\,452$) **Measurements** Episodes of hospitalization were observed as outcomes. Information on in-patient contacts, length of stay and diagnoses (International Classification of Diseases version 10) were assessed. Binary logistic regressions were conducted to estimate the associations between OMT exposure and the outcomes, crude and adjusted for the socio-economic status and smoking. **Findings** No significant differences were found in the overall proportion of hospitalization among OMT-exposed children, children of OMT-D and children of women with OUD [54.1%, 95% confidence interval (CI) = 47.3–60.1%; 47.3%, 95% CI = 33.9–61.1%; 51.8%, 95% CI = 40.7%–62.6%], while the proportion was significantly lower (35.8%, 95% CI = 35.7–35.8%) in the GP. There were no significant differences in risk of specific diagnoses between OMT-exposed children, children of OMT-D and children of women with OUD. In the adjusted analyses, differences between OMT-exposed and children in the GP were still present for infections and parasitic diseases (OR = 2.0, 95% CI = 1.4–2.7), diseases of the digestive system (OR = 1.7, 95% CI = 1.2–2.6) and diseases of the skin and subcutaneous tissue (OR = 1.9, 95% CI = 1.2–3.2). **Conclusion** This study did not find clear evidence for an increase in risk of morbidity during the first 3 years of life in children with prenatal opioid maintenance treatment exposure compared with children of women who discontinued such treatment before pregnancy or suffered from opioid use disorder without this treatment. Compared the general population, there appears to be an increased risk of hospitalizations for infectious, gastrointestinal and skin diseases.

Keywords Buprenorphine, child morbidity, health registries, hospitalization, long-term effects, methadone, opioid maintenance treatment, prenatal exposure.

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INTRODUCTION

Opioid maintenance therapy (OMT) is the recommended treatment for opioid dependence during pregnancy [1]. Patients in OMT receive long-acting opioid agonists (e.g. methadone or buprenorphine) in order to reduce craving for illicit opioids and to prevent relapse. Studies on the safety of these drugs for the unborn child focus mainly on birth parameters and short-term outcomes. Offspring exposed to OMT *in utero* have been shown to

have lower growth parameters at birth and higher rate of neonatal abstinence syndrome (NAS) when compared to the general population [2–4].

A few studies have attempted to address the effects of prenatal OMT exposure on the child's health beyond the perinatal period. Inconsistent findings regarding children's mental development following *in-utero* OMT exposure have been reported [5–8].

Even fewer studies have investigated the general morbidity and mortality among OMT-exposed children [9–11]. In a study from Western Australia, health outcomes during the first 5 years of life of children exposed to methadone, buprenorphine or naltrexone *in utero* were compared with a control group selected from the general population. Overall, the rates of hospital admissions were elevated both in children exposed to the two opioid agonists (methadone and buprenorphine) and the opioid antagonist (naltrexone) [10].

Previous studies on childhood morbidity after prenatal opioid exposure have focused mainly on children with NAS. NAS is a serious adverse event that could potentially influence the child's future health. Prenatal OMT exposure results in NAS in approximately 60–80% of neonates [12]. Maternal use of other substances that cause drug dependence may also result in NAS in the newborn [13]. The studies focusing on NAS are therefore not purely studies of consequences of OMT treatment. Generally, studies of children experiencing NAS found significantly increased rates of hospitalization during childhood compared to children in the general population [14–16].

In previous studies, OMT-exposed children or children with NAS have been compared to children in the general population. The OMT-exposed children are not only exposed to OMT drugs, but also to several other risk factors, such as maternal smoking and somatic and psychiatric illnesses as well as other unfavourable life-style factors. When studying OMT exposure, appropriate comparison groups are therefore needed to disentangle the effect of the drug from the effect of other risk factors and to avoid influence of unmeasured confounding. Children of pregnant women with indications for OMT but who were not in OMT during pregnancy could serve as such comparison group.

In the Czech Republic, nation-wide health registries with compulsory registration exist [17]. Using unique personalized identification numbers, it is possible to link data from the registries on an individual level. This approach gives us the opportunity to study large, unselected populations of women with opioid use disorders in or out of treatment without loss to follow-up [17].

The aims of this study were to examine morbidity in the first 3 years of life. Specifically, comparisons were made between the following groups.

1. Children prenatally exposed to OMT and:

(a) children of women who had used OMT before, but not during pregnancy (OMT discontinuers; OMT-D);
(b) children of women with opioid use disorders (OUD), who were not in OMT during pregnancy; and
(c) children of women in the general population of pregnant women (GP), without indications of opioid use disorders.

2. Children prenatally exposed to buprenorphine versus those exposed to methadone.

The hypothesis in the study was that OMT-exposed children will not have higher morbidity than the two relevant comparison groups, but higher morbidity than the general population. In addition, buprenorphine-exposed children might have lower morbidity compared to methadone-exposed children.

METHODS

Data from nation-wide health registries were used to investigate in-patient childhood morbidity. Linkage of data between the registries on reproductive health, addiction treatment, hospitalization and death was based on the personal identification numbers assigned to all individuals in the Czech Republic [17,18]. Identification numbers are assigned by the Municipal Registry Office shortly after the birth. It is used as an essential tool for the identification of the citizens across the public administration.

Data sources

In the Czech Republic, physicians are obliged by law to report data to the national health registries.

The National Register of reproduction health (NRRH)

The NRRH holds information about maternal health, life-style during pregnancy, demographic and socio-economics and information about delivery and the neonate, including birth parameters, congenital malformations and death.

The National Register of addiction treatment (NRAT)

The NRAT includes information about patients who receive OMT, e.g. date of initiation and termination of treatment and type of OMT drug.

OMT became available for treatment in Czech Republic in the late 1990s; methadone became available in 1997, buprenorphine in 2000 and a buprenorphine–naloxone combination in 2008 [19]. Methadone is provided only at specialized OMT clinics free of charge, while buprenorphine and buprenorphine–naloxone can be prescribed by all physicians irrespective of their specialization, and are

dispensed in pharmacies and typically fully paid for by the patients.

The National Register of in-patient treatment (NRIT)

The NRIT includes information on every episode of all types of hospitalizations, including information on dates of admission and discharge from hospital. Transfer to a different department during the same hospital stay is recorded as a separate hospitalization. Diagnoses in the discharge summary are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

Hospitals represent secondary health-care level. The primary level is represented by general practitioners for children and adolescents—each child is registered to one specific general practitioner. The general practitioners act as gate-keepers for in-patient treatment. Outside the general practitioners for children and adolescents' working hours, out-patient emergency units in hospitals refer patients to in-patient departments. Nearly all hospitals offering acute care have paediatric departments. The NRIT does not have information for patients who are only in contact with primary health-care services.

The information system on deaths (ISZEM)

The ISZEM is a general mortality register of the Czech Republic, holding time and cause of death for people with a permanent or long-term residence in the Czech Republic.

Exposure to OMT drugs during pregnancy

The start and end of pregnancy was assessed for women registered in NRRH. This information was linked to the NRAT to identify use of OMT drugs (methadone, buprenorphine or buprenorphine–naloxone) during pregnancy. Children were defined as prenatally exposed to OMT if their mother had received one of the OMT drugs during pregnancy (OMT-exposed group). None of the pregnant women switched between different OMT drugs during pregnancy.

Comparison groups

Children prenatally exposed to OMT were compared with three groups. The two most relevant comparison groups were children of pregnant women with indications for OMT but who were not in OMT during pregnancy. More specifically, group 1, 'OMT discontinuers (OMT-D)', were defined as children of women who used an OMT drug during the 360-day period before pregnancy start, but not during pregnancy, and group 2, 'opioid use disorders (OUD)', were defined as children of women hospitalized with a diagnosis of mental or behavioural disorder due to opioid use (ICD-10 code F11, all subcodes) during pregnancy, but who were not in OMT either 360 days before or during pregnancy. The third group 3 was represented by children of pregnant women without indications of opioid use disorders in the general population (GP).

Outcomes

Hospitalizations were used as a measure of morbidity. Information about hospitalizations of children was assessed for the time-period from discharge from the hospital after birth until the age of 3 years. Data from NRIT were used to assess information on all in-patient contacts, length of stay, primary and secondary ICD-10 diagnoses (chapter level I–XXI) at discharge. Where diagnoses were recorded for three or fewer cases, the data were not reported.

Study population and study period

The study population included all children born in the Czech Republic during the study period, 2000–14. Of these, 331 were children in the OMT group, 81 were in the OMT-D group and 104 in the OUD group. Children of women from the GP with no recorded history of opioid use disorder were the largest group (n = 1 556 583). Some of the children were born late in the study period and were excluded because they did not reach the age of 3 years (Fig. 1). Children who died by the age of 3 were also excluded, including two (0.6%) in the OMT group, none in the OMT-D and OUD groups and 997 (0.1%) in the GP group. Both of the OMT children who died during follow-up were exposed to buprenorphine and lived just below 1.5 years; only one of them was hospitalized for diseases of respiratory system (ICD-10 code J03). The final study population consisted of 218 children in the OMT group, 55 in the OMT-D group, 85 in the OUD group and 1 238 452 in the GP group.

Other variables

Background characteristics of the pregnant women were obtained from NRRH as described above [18].

Analysis strategy and statistics

Descriptive statistics [mean, median and interquartile range (IQR)] were used to present the proportion of hospitalized children, frequency of hospitalizations, length of hospital stay and number of diagnoses (primary and secondary diagnoses) per child in each group for children who reached age of 3. Negative binominal regression analysis was used to calculate the risk for hospitalization among OMT-exposed children compared to children of OMT-D women, women with OUD and women from the GP. For the risk associated with the exposure to methadone versus buprenorphine and buprenorphine–naloxone,

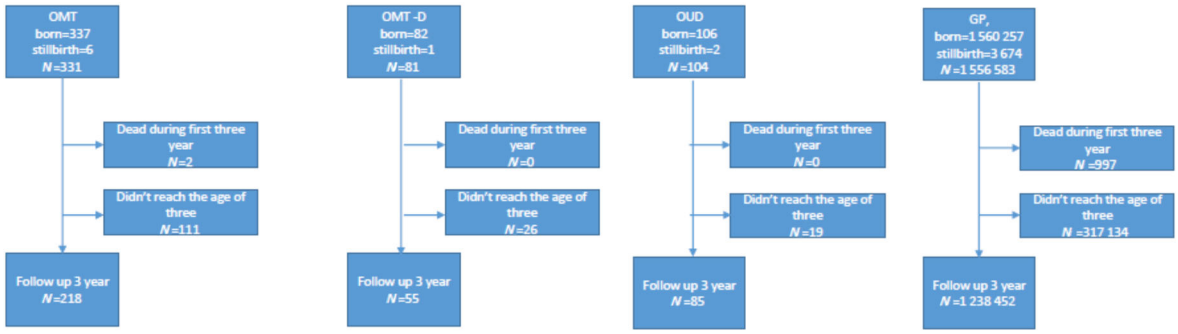

Figure 1 Children included in the study. [Colour figure can be viewed at wileyonlinelibrary.com]

binary logistic regression with the outcome of the child being hospitalized (yes/no) was performed.

Next, the proportion of children hospitalized with different ICD-10 chapter diagnoses during the period after discharge following birth and until the age of 3 years was calculated. The population of children who reached 3 years of age was used as the denominator. Confidence intervals (CI) for proportion were calculated using the continuity correlated with the score interval method [20]. To control for relevant maternal background characteristics, binary logistic regression for the categorical dependent variables (diagnoses yes/no) for each diagnosis chapter separately was performed. Unadjusted and adjusted odds ratio (aOR) with 95% CI were presented for the OMT group compared to the OMT-D, OUD and GP groups. Only significant comparisons from unadjusted analyses were adjusted for maternal age, marital status, education and smoking.

The level of statistical significance for all analyses was set at $P < 0.05$ using two-tailed comparisons. Statistical analyses were conducted using SPSS for Windows, version 23, and STATA 14.

Significant associations were further examined in subanalyses stratified by gender and the presence of diseases originating in perinatal period.

Ethics

The study was approved by the Institutional Review Board of the General University Hospital in Prague (IRB00002705).

RESULTS

Background characteristics

Table 1 illustrates maternal background characteristics in the OMT, OMT-D, OUD and GP groups. OMT, OMT-D and OUD were similar in all characteristics, with the exception of the OUD women being markedly younger. However, each of these groups had more unfavourable life-style characteristics than the GP.

Hospitalization

By 3 years of age, 54.1% of OMT-exposed children, 47.3% of children of OMT-D and 51.8% of children of women with OUD had been hospitalized at least once, compared to 35.8% of children in the GP (Table 2). Regarding the number of hospitalizations, length of stay and number of diagnoses, OMT-exposed children and children in the OMT-D and OUD groups were similar, but they had longer stays and more diagnoses than children in the GP. The children born by OMT-D had worse outcomes than the OMT-exposed children regarding the number of hospitalizations ($P = 0.001$) and length of stay ($P < 0.001$).

When the OMT-exposed group was compared to the GP, the risk of hospitalization was increased for the OMT-exposed (aOR = 1.6, 95% CI = 1.2–2.1). Significant differences were also found for length of stay (17.4 versus 8.6 mean days, $P < 0.001$) and number of diagnoses (3.9 versus 3.0, $P < 0.001$) (Table 2).

The risk of hospitalization was lower for buprenorphine-exposed children compared to methadone-exposed (aOR = 0.6, 95% CI = 0.3–1.0) (Table 3). The buprenorphine-exposed children also had significantly shorter hospital stays compared to children prenatally exposed to methadone.

Diagnoses

Table 4 shows the proportions of children in the different groups who had received the different diagnoses until the age of 3. The proportions of children in the OMT-exposed group and the OMT-D and OUD groups with diagnoses were higher than in the general population for almost all diagnosis chapters (Table 4). The most common diagnosis

Table 1 Socio-economic characteristics of pregnant women in opioid maintenance therapy compared to the OMT-D, OUD and GP groups in the Czech Republic.

	Buprenorphine			*Methadone*			*OMT*			*OMT-D*			*OUD*			*GP*		
	n	*%*	*95% CI*	*n*	*%*	*95% CI*	*n*	*%*	*95% CI*	*n*	*%*	*95% CI*	*n*	*%*	*95% CI*	*n*	*%*	*95% CI*
Total number	91			127			218			55			85			1 238 452		
Age, years																		
≤ 24	31	34.1	24.7–44.8	43	33.9	25.9–42.9	74	33.9	27.8–40.7	19	34.5	22.6–48.7	61	71.8	60.8–80.7	264 822	21.4	21.3–21.5
25–29	37	40.7	30.6–51.5	53	41.7	33.2–50.8	90	41.3	34.7–48.1	25	45.5	32.2–59.3	16	18.8	11.5–29.1	469 583	37.9	37.8–38.0
30–34	22	24.2	16.1–34.5	25	19.7	13.4–27.9	47	21.6	16.4–27.7	9	16.4	8.2–29.3	4	4.7	1.5–12.3	363 229	29.3	29.2–29.4
≥ 35	1	1.1	0.1–6.8	6	4.7	1.9–10.4	7	3.2	1.4–6.8	2	3.6	0.6–13.6	2	2.4	0.4–9.0	129 678	10.5	10.4–10.5
Marital status																		
Not married	70	76.9	66.7–84.8	100	78.4	70.4–85.3	170	78.0	71.8–83.2	40	72.7	58.8–83.5	69	81.2	70.9–88.5	388 288	31.4	31.3–31.4
Married	15	16.5	9.8–26.1	25	19.7	13.4–27.9	40	18.3	13.6–24.3	10	18.2	9.5–31.4	8	9.4	4.4–18.2	822 761	66.4	66.4–66.5
Unknown	6	6.6	2.7–14.3	2	1.6	0.3–6.1	8	3.7	1.7–7.4	5	9.1	3.4–20.7	8	9.4	4.4–18.2	27 403	2.2	2.2–2.2
Education																		
Primary	41	45.1	34.7–55.8	74	58.3	49.2–66.8	115	52.8	45.9–59.5	33	60.0	45.9–72.7	48	56.5	45.3–67.1	137 688	11.1	11.1–11.2
Secondary	45	49.5	38.9–60.1	48	37.8	29.5–46.9	93	42.7	36.1–49.5	18	32.7	21.0–46.8	33	38.8	28.6–50.0	848 295	70.9	70.8–71.0
University	3	3.3	0.9–10.0	0	0.0	0.0–2.9	3	1.4	0.4–4.3	1	1.8	0.1–11.0	0	0.0	0.0–4.2	185 951	15.0	15.0–15.1
Unknown	2	2.2	0.4–8.5	5	3.9	1.5–9.4	7	3.2	1.4–6.8	3	5.5	1.4–16.1	4	4.7	1.5–12.3	66 518	5.4	5.3–5.4
Using of addictive substances during pregnancy																		
Smoking	33	36.3	26.6–47.1	54	42.5	33.9–51.6	87	39.9	33.4–46.8	23	41.8	28.9–55.9	32	37.6	27.6–48.9	73 575	5.9	5.9–6.0
Alcohol	3	3.3	0.9–10.0	5	3.9	1.5–9.4	8	3.7	1.7–7.4	2	3.6	0.6–13.6	6	7.1	2.9–15.3	1626	0.1	0.1–0.1
Illicit drugs	35	38.5	28.6–49.3	52	40.9	32.4–50.0	87	39.9	33.4–46.8	22	40.0	27.3–54.1	36	42.4	31.9–53.5	1976	0.2	0.2–0.2

OMT = women in opioid maintenance therapy; OMT-D= women who had been in OMT before pregnancy but not in pregnancy (OMT discontinuers); OUD = women hospitalized with a diagnosis of mental or behavioural disorder due to opioid use (ICD-10 code F11, all subcodes) during pregnancy; GP = pregnant women from the general population; CI = confidence interval.

Table 2 Hospital admissions in children (0–3 years) of women in opioid maintenance therapy compared to the OMT-D, OUD and GP groups in the Czech Republic.

	OMT	*OMT-D*	*OUD*	*OMT versus OMT-D*	*OMT versus OUD*	*GP*	*OMT versus GP*
Children who reached age of 3 years, *n*	218	55	85			1 238 452	
				OR[a] (95% CI)	OR[a] (95% CI)		OR[a] (95% CI)
Hospitalized children, *n* (%, CI)	118 (54.1, 47.3–60.1)	26 (47.3, 33.9–61.1)	44 (51.8, 40.7–62.6)	1.3 (0.7–2.4)	1,1 (0.7–1.8)	442 862 (35.8, 35.7–35.8)	**2.1 (1.6–2.8)**
				adj[b] 1.3 (0.7–2.3)	adj[b] 1.2 (0.7–2.1)		**adj[b] 1.6 (1.2–2.1)**
				P[c]	P[c]		P[c]
Number of hospitalizations, mean, median, IQR	2.0, 2.0, 1.0–2.3	3.5, 1.5, 1.0–3.0	2.2, 2.0, 1.0–2.8	0.001	0.400	1.8, 1.0, 1.0–2.0	0.100
Length of stay in days, mean, median, IQR	17.4, 10.0, 4.0–21.0	41.8, 8.0, 4.0–23.5	14.4, 7.7, 4.0–16.5	**< 0.001**	0.297	8.6, 4.0, 2.0–9.0	**< 0.001**
Number of all diagnoses mean, median, IQR	3.9, 3.0, 2.0–5.0	4.5, 3.0, 1.8–5.0	4.1, 3.0, 2.0–5.0	0.378	0.672	3.0, 2.0, 1.0–4.0	**< 0.001**

Excluded ICD 10 codes Z37 and Z38 diagnoses and birth hospitalization. OMT = children exposed to opioid maintenance therapy; OMT-D = children of women who had been in OMT before pregnancy but not in pregnancy (OMT discontinuers); OUD = children of women hospitalized with a diagnosis of mental or behavioural disorder due to opioid use (ICD-10 code F11, all subcodes) during pregnancy; GP = children of women from the general population; CI = confidence interval; IQR = interquartile range. [a]Odds ratios (ORs) from binary logistic regression of the child being hospitalized; [b]adj = adjusted for maternal age, education and smoking status during pregnancy; [c]*P*-value from negative binominal regression analyses.

Table 3 Hospital admissions in children (0–3 years) of women in opioid maintenance therapy using buprenorphine during pregnancy compared compared to the women using methadone in the Czech Republic.

	Buprenorphine[a]	*Methadone*	*Buprenorphine*[a] *versus methadone*
Children who reached age of 3 years, *n*	91	127	
			OR[b] (95% CI)
Hospitalized children, *n* (%, CI)	40 (44.0, 33.7–54.3)	78 (61.4, 52.3–69.8)	**0.5 (0.3–0.9)**
			adj[c] **0.6 (0.3–1.0)**
			P[d]
Number of hospitalizations, mean, median, IQR	1.9, 2.0, 1.0–2.0	2.1, 2.0, 1.0–3.0	0.497
Length of stay in days, mean, median, IQR	12.0, 6.5, 3.0–15.8	20.2, 11.0, 4.8–27.3	**0.008**
Number of all diagnoses mean, median, IQR	3.7, 3.0, 2.0–4.0	4.0, 3.0, 2.0–5.0	0.496

Excluded ICD 10 codes Z37 and Z38 diagnoses and birth hospitalization. CI = confidence interval; IQR = interquartile range. [a]Buprenorphine (n = 82) and buprenorphine–naloxone combination (n = 9). [b]Odds ratios (ORs) from binary logistic regression of the child being hospitalized; [c]adj = adjusted for maternal age, education and smoking status during pregnancy; [d]*P*-value from negative binominal regression analyses.

chapter was diseases of the respiratory system (chapter X) and certain infections and parasitic diseases (chapter I). The proportion receiving these diagnoses in the OMT exposed children were 24.3 and 21.6%, respectively, compared to 16.3 and 8.9% in the GP.

The unadjusted logistic regression analysis showed no statistically significant differences between the OMT-exposed and OMT-D and OUD groups (Table 4). For the majority of diagnoses there were differences in risk in the unadjusted analysis when comparing OMT-exposed to the GP. After adjustment (a), there were still increased ORs of infectious and parasitic diseases (aOR = 2.0, 95% CI = 1.4–2.7), diseases of the digestive system (aOR = 1.7, 95% CI = 1.2–2.6) and diseases of the skin and subcutaneous tissue (aOR = 1.9, 95% CI = 1.2–3.2). The risk of having a diagnosis in the diagnosis chapter of certain conditions originating in the perinatal period and in symptoms, signs and abnormal clinical laboratory findings were also significantly increased.

When comparing diagnoses, there were significant differences between children prenatally exposed to buprenorphine and methadone only for certain conditions originating in the perinatal period (Table 5).

Results of the subanalyses of diagnoses generally supported our main findings. In the analysis stratified on either gender or presence of conditions originating in the perinatal period, the results were in the same direction as in the main analysis (Supporting information, Table S1).

DISCUSSION

There was no increased risk of morbidity for the OMT-exposed children compared to children in the OMT-D and OUD groups, as measured by hospitalization and the prevalence of ICD-10 diagnoses. When compared to the GP group, children in the OMT group had a higher risk of hospitalization and received more diagnoses by the age of 3. More specifically, the OMT group had a higher risk of infectious, digestive diseases, diseases of the skin and subcutaneous tissue, as well as conditions originating in the perinatal period, compared to the GP group.

The strong and unique aspects of our study reside in using relevant comparison groups. This study compared OMT-exposed children not only to children in the GP but also to OMT discontinuers and to children of women with OUD. These women are more similar to women in OMT treatment regarding their socio-demographic characteristics and life-style than to women in the general population. Comparison among similar groups may contribute to increased control over unmeasured residual confounding. The comparable risk found in children with different prenatal OMT exposure suggests that it is not OMT treatment itself that is associated with the increased morbidity in OMT-exposed children. Kelty *et al.*'s previous finding, that both prenatal exposure to opioid agonists and antagonists increase the risk of morbidity, also points in the direction that the association is not caused by OMT drugs [10]. The implications of the study findings might be that that other risk factors could be associated with opioid use disorders as opposed to use of OMT drugs during pregnancy, which result in a higher risk of morbidity in all the groups of women with opioid use disorders (OMT, OMT-D and OUD) compared to the GP.

In concordance with this study, Kelty *et al.* also reported a higher risk of hospitalization for skin and subcutaneous diseases in OMT-exposed children [10]. A study focusing on children with NAS [15] also found an increased risk of these ICD-10 diagnostic chapters [15].

Increased morbidity in OMT-exposed children, as well as in children in the comparison groups, can be explained by multiple factors. A possibility is that the excess of infectious, digestive and skin diseases could be attributed to a higher risk of infections in general due either to increased exposure to microbial pathogens or a weak immune

Table 4 Binary logistic regression comparing children of women in opioid maintenance therapy compared to the OMT-D, OUD and GP groups in the Czech Republic.

Chapter of ICD-10 diagnoses	*OMT (n = 218)* *Cases n (%)*	*OMT-D (n = 55)* *Cases n (%)*	*OUD (n = 85)* *Cases n (%)*	*GP (n = 1 238 452)* *Cases n (%)*	*OMT versus OMT-D (ref.)* *OR unadjusted (95% CI)*	*OMT versus OUD (ref.)* *OR unadjusted (95% CI)*	*OMT versus GP (ref.)* *OR unadjusted (95% CI)*	*OMT versus GP (ref.)* *OR adjusted[a] (95% CI)*
I. Certain infectious and parasitic diseases (A00–B99)	47 (21.6)	9 (16.4)	14 (16.5)	110 383 (8.9)	1.4 (0.6–3.1)	1.4 (0.7–2.7)	**2.8 (2.0–3.9)**	**2.0 (1.4–2.7)**
III. Diseases of the blood, blood-forming organs and certain disorders involving the immune mechanisms (D50–D89)	13 (6.0)	2 (3.6)	5 (5.9)	34 680 (2.8)	1.7 (0.4–7.7)	1.0 (0.4–2.9)	**2.2 (1.3–3.9)**	1.4 (0.8–2.4)
IV. Endocrine, nutritional and metabolic diseases (E00–E90)	7 (3.2)	3 (5.5)	5 (5.9)	50 140 (4.0)	0.6 (0.1–2.3)	0.5 (0.2–1.7)	0.8 (0.4–1.7)	[b]
VII. Diseases of the eye and adnexa (H00–H59)	7 (3.2)	1 (1.8)	2 (2.4)	18 013 (1.5)	1.8 (0.2–14.9)	1.4 (0.3–6.8)	**2.2 (1.1–4.8)**	1.6 (0.7–3.3)
VIII. Diseases of the ear and mastoid process (H60–H95)	8 (3.7)	1 (1.8)	7 (8.2)	27 323 (2.2)	2.1 (0.3–16.8)	0.4 (0.2–1.2)	1.7 (0.8–3.3)	[b]
X. Diseases of the respiratory system (J00–J99)	53 (24.3)	12 (21.8)	23 (27.1)	201 825 (16.3)	1.2 (0.6–2.3)	0.9 (0.5–1.5)	**1.7 (1.2–2.2)**	1.1 (0.8–1.5)
XI. Diseases of the digestive system (K00–K93)	30 (13.8)	4 (7.3)	10 (11.8)	77 917 (6.3)	2.0 (0.7–6.0)	1.2 (0.6–2.6)	**2.4 (1.6–3.5)**	**1.7 (1.2–2.6)**
XII. Diseases of the skin and subcutaneous tissue (L00–L99)	18 (8.3)	5 (9.1)	4 (4.7)	35 017 (2.8)	0.9 (0.3–2.5)	1.8 (0.6–5.6)	**3.1 (1.9–5.0)**	**1.9 (1.2–3.2)**
XIV. Diseases of the genitourinary system (N00–N99)	8 (3.7)	3 (5.5)	5 (5.9)	44 674 (3.6)	0.7 (0.2–2.6)	0.6 (0.2–1.9)	1.0 (0.5–2.1)	0.9 (0.5–1.9)
XVI. Certain conditions originating in the perinatal period (P00-P96)	32 (14.7)	6 (10.9)	11 (12.9)	35 882 (2.9)	1.4 (0.6–3.6)	1.2 (0.6–2.4)	**5.8 (4.0–8.4)**	**4.6 (3.1–6.7)**
XVII. Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	13 (6.0)	5 (9.1)	6 (7.1)	43 355 (3.5)	0.6 (0.2–1.9)	0.8 (0.3–2.3)	1.7 (1.0–3.1)	[b]
XVIII. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	40 (18.3)	8 (14.5)	9 (10.6)	118 551 (9.6)	1.3 (0.6–3.0)	1.9 (0.9–4.1)	**2.1 (1.5–3.0)**	**1.5 (1.1–2.1)**
XIX. Injury, poisoning and certain other consequences of external causes (S00–T98)	21 (9.6)	4 (7.3)	5 (5.9)	79 796 (6.4)	1.4 (0.4–4.1)	1.7 (0.6–4.7)	1.5 (1.0–2.4)	[b]
XXI. Factors influencing health status and contact with health services (Z00–Z99)	19 (8.7)	5 (9.1)	7 (8.2)	56 426 (4.6)	1.0 (0.3–2.7)	1.1 (0.4–2.6)	**2.0 (1.2–3.2)**	1.5 (0.9–2.4)

OMT = children exposed to opioid maintenance therapy; OMT-D children of women who had been in OMT before pregnancy but not in pregnancy (OMT discontinuers); OUD = children of women hospitalized with a diagnosis of mental or behavioural disorder due to opioid use (ICD-10 code F11, all subcodes) during pregnancy; GP = children of women from the general population; CI = confidence interval. OR 95% CI = odds ratio with 95% confidence interval. [a]Adjusted for maternal age, education and smoking status during pregnancy; [b]adjusted analyses not performed because there were no significant results in the unadjusted analyses.

Table 5 Binary logistic regression comparing children of women using buprenorphine compared to women using methadone in the Czech Republic.

Chapter of ICD-10 diagnoses	*Buprenorphine[a] (n = 91) Cases* n *(%, 95% CI)*	*Methadone (n = 127) Cases* n *(%, 95% CI)*	*Buprenorphine[a] versus methadone (ref.) OR unadjusted (95% CI)*
I. Certain infectious and parasitic diseases (A00–B99)	16 (17.6, 10.7–27.3)	31 (24.4, 17.4–33.0)	0.7 (0.3–1.3)
III. Diseases of the blood, blood-forming organs and certain disorders involving the immune mechanisms (D50–D89)	6 (6.6, 2.7–14.4)	7 (5.5, 2.4–11.4)	1.2 (0.4–3.7)
IV. Endocrine, nutritional and metabolic diseases (E00–E90)	3 (3.3, 0.9–10.0)	4 (3.1, 1.0–8.4)	1.0 (0.2–4.8)
VII. Diseases of the eye and adnexa (H00–H59)	1 (1.1, 0.01–6.8)	6 (4.7, 1.9–10.4)	0.2 (0.0–2.9)
VIII. Diseases of the ear and mastoid process (H60–H95)	0 (0.0, 0.0–4.0)	8 (6.3, 3.0–12.4)	[b]
X. Diseases of the respiratory system (J00–J99)	18 (19.8, 12.5–29.7)	35 (27.6, 20.2–36.3)	0.6 (0.3–1.2)
XI. Diseases of the digestive system (K00–K93)	13 (14.3, 8.1–23.6)	17 (13.4, 8.2–20.8)	1.1 (0.5–2.3)
XII. Diseases of the skin and subcutaneous tissue (L00–L99)	6 (6.6, 2.7–14.4)	12 (9.4, 5.2–16.3)	0.7 (0.2–1.9)
XIV. Diseases of the genitourinary system (N00–N99)	3 (3.3, 0.9–10.0)	5 (3.9, 1.5–9.4)	0.8 (0.2–3.6)
XVI. Certain conditions originating in the perinatal period (P00–P96)	8 (8.8, 4.2–17.1)	24 (18.9, 12.7–27.0)	**0.4 (0.2–1.0)**[c]
XVII. Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	5 (5.5, 2.0–12.9)	8 (6.3, 3.0–12.4)	0.9 (0.3–2.7)
XVIII. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	13 (14.3, 8.1–23.6)	27 (21.3, 14.7–29.6)	0.6 (0.3–1.3)
XIX. Injury, poisoning and certain other consequences of external causes (S00–T98)	7 (7.7, 3.4–15.7)	14 (11.0, 6.4–18.1)	0.7 (0.3–1.7)
XXI. Factors influencing health status and contact with health services (Z00–Z99)	7 (7.7, 3.4–15.7)	12 (9.4, 5.2–16.3)	0.8 (0.3–2.1)

OR 95% CI = odds ratio with 95% confidence interval. [a]Buprenorphine (n = 82) and buprenorphine naloxone combination (n = 9); [b]zero cases; [c]adjusted OR = 0.4 (0.2–1.0), P = 0.049, adjusted for maternal age, education and smoking status during pregnancy.

system. A weaker immune system might be due to a direct effect of opioids on the immune cells or to poorer maternal health compared to the general pregnant population [21]. Findings from studies on the opioid effects on the immune system have been inconclusive, nor is it clear if there is an effect on the developing immune system of the fetus [22]. Our findings did not support a direct influence on the immune system of OMT drugs, as there was no difference between the OMT group and the OMT discontinuers. Higher morbidity in children born to substance-using mothers due to epigenetic mechanism during intrauterine development has also been suggested as an explanation for the weaker immune systems of exposed children [22].

Aside from prenatal exposure to opioid drugs, we also cannot ignore the importance of pre- and postnatal risk factors, including poor nutrition, hygiene, parenting and other drug use. Psychosocial stress can also contribute to higher vulnerability in the context of allostatic load during pregnancy [23,24].

Not surprisingly, our study found a higher risk of conditions originating in the perinatal period in the OMT-exposed group when compared to the GP. It is well documented that OMT-exposed newborns have a higher risk of preterm birth, growth retardation and NAS compared to the general population.

The risk for conditions originating in the perinatal period was lower among OMT children exposed to buprenorphine compared to those exposed to methadone. This is in contrast to our previous findings regarding no differences in neonatal outcomes in children prenatally exposed to buprenorphine versus methadone [18]. The diagnostic chapter of conditions originating in the perinatal period includes more disorders than were included in our previous study, and some of these can be diagnosed retrospectively. In addition, children exposed to methadone had longer hospital stays than buprenorphine-exposed children, which can be partly explained by longer treatment of more severe NAS, as previously reported by others in newborns exposed to methadone [25].

The few existing studies on long-term outcomes found an increased frequency of mental and behavioural disorders among NAS children or children of OMT-exposed women [10,15]. It was not possible to examine mental and behavioural disorders in this study, as these conditions are typically diagnosed at a later stage of the child's development.

Methodological consideration

By accessing national registries on reproductive health, addiction treatment, hospitalization and death, it was possible to establish a national cohort and examine their longitudinal data. Therefore, selection bias is less of a problem than in many clinical samples. In addition, health registries identify larger samples than can feasibly be included in clinical studies.

Using information from the registries reduces the risk of recall bias. However, some important information can be under-reported or reported in insufficient format in the registries, e.g. use of alcohol and illicit drugs by pregnant women. Further, information on nutrition or infections during pregnancy is lacking. An important limitation is the lack of information on NAS in the newborn, which could be a mediator of the observed association between OMT exposure and childhood morbidity.

Mortality was slightly higher among OMT-exposed children than among children in comparison groups (0.6 versus 0% in the observation period). It is unknown whether the cause of death could be linked to *in-utero* exposure to OMT drugs, but hospital data do not suggest that any of the children had serious disease prior to death. Nevertheless, the mortality rate was so low that it would not influence the estimates.

While opioid-dependent women in the Czech Republic can receive methadone free of charge, they must pay a substantial price for buprenorphine. Bias is likely, as women who are able to pay for buprenorphine probably belong to a higher socio-economic class and/or they are under-dosed in order to limit the expenses. Their background characteristics might suggest that the buprenorphine-using women had higher education and smoked to a lesser extent than the methadone-using women, but the results were not significant. Unfortunately, the registry does not contain information concerning the OMT drugs dose.

The current study used data from the hospitalization registry on frequency and diagnosis set by the physicians at hospital discharge reports to describe morbidity of the children prenatally exposed to OMT, from birth to 3 years of age. Out-patient morbidity, which probably represents a substantial proportion of morbidity, is missing in our analysis. Nonetheless, the more serious health problems that required hospitalization are included.

CONCLUSION

In this nation-wide cohort of pregnant women with opioid use disorders, no statistically significant differences were observed in childhood morbidity between children of women in OMT during pregnancy, OMT discontinuers or women with OUD during pregnancy. Compared to children in the general population, OMT-exposed children had higher risk of infections, digestive diseases and diseases of the skin and subcutaneous tissue, but the risk estimates are probably confounded by unmeasured life-style factors associated with opioid use disorders. These findings need to be replicated in other countries, preferably in larger study samples.

Declaration of interests

None.

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Supporting Information

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

Table S1 Binary logistic regression comparing children of women in opioid maintenance therapy to the general population in the Czech Republic. Stratified analyses on gender and certain conditions originating in the perinatal period.