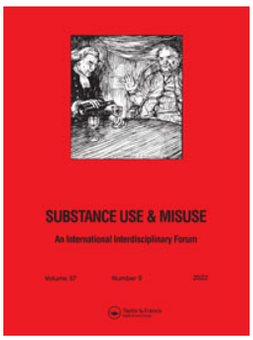

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ORIGINAL ARTICLE

Buprenorphine Compared with Methadone in Pregnancy: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Illicit opioid use in pregnancy is associated with adverse maternal, neonatal, and childhood outcomes. Opioid substitution is recommended, but whether methadone or buprenorphine is the optimal agent remains unclear. *Methods:* We searched EMBASE, PubMed, Web of Science, Scopus, Open Gray, CINAHL and the Cochrane Central Registry of Controlled Trials (CENTRAL) from inception to April 2020 for randomized controlled trials (RCTs) and cohort studies comparing methadone and buprenorphine treatment for opioid-using mothers. Included studies assessed maternal and or neonatal outcomes. We used random-effects meta-analyses to estimate summary measures for outcomes and report these separately for RCTs and cohort studies. *Results:* Of 408 abstracts screened, 20 papers were included (4 RCTs, 16 cohort, 223 and 7028 participants respectively). All RCTs (4/4) had a high risk of bias and median (IQR) Newcastle Ottawa Scale for cohort studies was 7.5 (6–9). In both RCTs and cohort studies, buprenorphine was associated with; greater offspring birth weight (weighted mean difference [WMD] 343 g (95% CI: 40–645 g) in RCT and 184 g (95% CI: 121–247 g) in cohort studies); body length at birth (WMD 2.28 cm (95% CI: 1.06–3.49 cm) in RCTs and 0.65 cm (95% CI: 0.31–0.98 cm) in cohort studies); and reduced risk of prematurity (risk ratio [RR] 0.41 (95% CI: 0.18–0.93) in RCTs and 0.63 [95% CI: 0.53–0.75] in cohort studies) when compared to methadone. All other clinical outcomes were comparable. *Conclusions:* Compared to methadone, buprenorphine was consistently associated with improved birthweight and gestational age, however given potential biases, results should be interpreted with caution.

KEYWORDS
Methadone; buprenorphine; pregnancy; opioid replacement

Introduction

Opioid use is common worldwide and is a growing public health challenge. In the United States of America, estimates of opioid use for non-medical reasons in 2019 was 10.3 million people (3.7% of the adult population), with approximately 745,000 people (0.3% of the adult population) consuming heroin every year (Substance Abuse & Mental Health Services Administration, 2020). The widespread adverse effects of illicit opioid use on maternal and child health are widely recognized (Stover & Davis, 2015). A multi-faceted public health response to opioid use in pregnancy is required to archive the World Health Organization's sustainability development goals of improving maternal and offspring health (International Expert Group on Drug Policy Metrics, 2018).

Pregnancy is recognized as an opportunity to change lifestyle behaviors (Cooper et al., 2017), and whilst abstinence from opioids during pregnancy is ideal, withdrawal from opioids during pregnancy is not recommended (National Institute for Health & Clinical Excellence, 2006; World Health Organisation, 2014). Opioid pharmacotherapy programs were established in the 1960s to integrate controlled opioid therapy with obstetric care, and social health interventions (Dole & Nyswander, 1965) and have led to reductions in overdoses (Schwartz et al., 2013), reduced recidivism, and reduced blood born virus transmission (American Society of Addicition Medicine, 2015). Opioid use in pregnancy carries a risk of neonatal abstinence syndrome (NAS), a collection of gastrointestinal, neurological, and behavioral symptoms following the abrupt cessation of opioids after delivery (American Society of Addicition Medicine, 2015). The balance between the risk of NAS and uncontrolled illicit opioid use favors opioid agonist therapies in pregnancy (National Institute for Health & Clinical Excellence, 2006; US Department for Health & Human Services, 2018; World Health Organisation, 2014).

Methadone is commonly used as an opioid agonist medication. Methadone therapy aims to provide stability of opioid levels, prevent withdrawal cycles, and improve engagement with obstetric care and neonatal outcomes, but is limited by stringent observation protocols and risk of overdose (Finnegan et al., 1977; National Institute for Health & Clinical Excellence, 2006). Buprenorphine is a more recently developed opioid agonist therapy and is an alternative to methadone. Buprenorphine is a partial opioid

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receptor agonist which has a ceiling effect on respiratory depression (limiting harm following overdose), a more flexible dosing design, and may have a more favorable neonatal opioid withdrawal profile when compared to methadone (White & Lopatko, 2007).

Previous meta-analyses have investigated differences between opioid agonist therapies, but have either included only RCTs (Minozzi et al., 2020), or RCTs plus cohort studies from over 5 years ago (Brogly et al., 2014; Zedler et al., 2016). Since 2015, five large cohort studies (~3000 patients) have been published (Bier et al., 2015; Brogly et al., 2018; Meyer et al., 2015; Nechanská et al., 2018; Tolia et al., 2018). Inclusion of these cohort studies will enable further triangulation of evidence given the limited evidence available from RCTs and previous smaller observational cohorts. The objective of this review was to systematically review all the published evidence to determine the optimal opioid substitution therapy in pregnancy.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was followed for reporting this systematic review and meta-analysis (Supplementary Table 1) (Moher et al., 2009). The protocol was registered with PROSPERO (CRD42020173882). We defined the research question in accordance with the PICO format (population, intervention, comparator, and outcomes) (Supplementary Table 2). The population of interest was patients taking opioid agonists whilst pregnant and their offspring. The intervention was buprenorphine drug therapy (with or without naloxone), and the comparator was methadone drug therapy. Maternal outcomes were side-effects associated with treatment, maintenance on treatment, illicit drug use, death, and mode of delivery. Offspring outcomes were stillbirth, birthweight, growth (total body length at birth and head circumference at birth, small for gestational age), prematurity, opioid withdrawal treatment, hospital admission duration, death, congenital anomalies, and childhood development. Full details of outcomes are shown in Supplementary Table 3.

We conducted a systematic search of EMBASE, PubMed, Web of Science, Scopus, Open Gray, CINAHL and the Cochrane central Registry of Controlled Trials (CENTRAL) from inception for April 2020 using a search strategy led by a senior university librarian, as shown in Supplementary Table 4. Eligible studies were full-text RCTs and observational cohort studies comparing methadone and buprenorphine and reporting maternal and or neonatal outcomes. We included cohort studies in accordance with Cochrane guidance (Reeves et al., 2022), to provide evidence of the effects (benefit or harm) of interventions for which only a small number of randomized trials are available (or are likely to be available). We excluded case-reports, case-series, case-control studies, and editorials. We limited our results to human studies. Non-English studies were translated using Google Translate.

Screening of titles was conducted using the Covidence software platform (v2619). One reviewer (MK) conducted the search and removal of duplications. Two reviewers (MK and YC) independently reviewed studies for eligibility by screening titles, abstracts, and subsequently full texts. Any disagreement was settled by discussion with a third reviewer (LH). One reviewer conducted data extraction, and assessment of bias (MK). A second reviewer (LH) independently extracted data for a sample of the trials (3 RCTs, and 2 cohort studies), to verify data entry standards. No significant differences were seen in data entry. The data were extracted into an Excel spreadsheet and analyzed in R (version 4.0.3), using the package "meta."

Assessment of risk of bias was performed using the Newcastle Ottawa Scale (Wells et al., 2014) for cohort studies and revised Cochrane Risk-of-Bias (RoB 2) tool for RCTs (Sterne et al., 2019). The Newcastle Ottawa Scale consists of three domains to assess the quality and risk of bias. These are: selection, comparability, and outcome assessment. Each cohort study was given a rating of stars for each domain with a maximum star rating of 4 for selection, 2 for comparability and 3 for outcome, with a greater number of stars reflecting a lower risk of bias. For RCTs, the RoB 2 reporting template was used to score each outcome as: "low risk," "some concern," or "high risk." The overall risk of bias is "low" if all domains are low risk, "some concerns" if some concerns are raised but these are not high risk, and "high risk" if any domain has high risk or there are multiple domains with some concerns. Data on risk of bias and overall quality assessment are presented in Supplementary Tables 5 and 6.

Results for RCT and cohort studies were analyzed separately (Reeves et al., 2022). We used a random effects model (DerSimonion & Laird model) due to heterogeneity between studies. For binary outcomes, we calculated risk ratios. For continuous outcomes we used weighted mean differences. Uncertainty of the estimates (relative risk [RR] and weighted mean difference [WMD]) was expressed by calculating the 95% confidence interval [CI] The I^2 statistic was used to assess study heterogeneity. The I^2 represents the percentage of variance across studies attributable to heterogeneity rather than change and is presented alongside each forest plot for both RCTs and cohort studies. To investigate publication bias we produced a funnel plot if the number of pooled studies was greater than 10 (Supplementary Figure 1). We used adjusted estimates where they were available for cohort studies. As adjusted estimates were only available for 8 of 16 cohort studies, for a total of four outcomes (Table 1), we present the primary results as unadjusted analyses. Estimates for the pooled, adjusted analyses (where available) are included in Supplementary Table 7.

Results

Our search strategy identified 803 studies. After the removal of duplicates, 404 studies were screened for inclusion. Four

Table 1. Studies of buprenorphine versus methadone maintenance treatment and maternal/neonatal outcomes.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Bier et al., 2015 USA	1996–2014	Retrospective cohort study	220 165 methadone 55 buprenorphine	Developmental Pediatric clinic, USA	Inclusion: All offspring born in clinic during study period Exclusion: Not specified	Total birth weight of offspring: methadone 2751g (SD ± 599), buprenorphine 2895g (SD ± 569) Gestational age at birth: methadone 37.5weeks (SD ± 3), buprenorphine 38weeks (SD ± 3) Prematurity: methadone 31 (19%), buprenorphine 5 (9%) Treatment for NAS: methadone 145 (88%), buprenorphine 45 (82%) Length of offspring hospital admission: methadone 39.9 (SD ± 24.3) buprenorphine 21 (SD ±13) Cesarean section rate: methadone 45 (27%), buprenorphine (18%) Development assessment: Bayley Mental Development Index Low dose methadone: 96.6(SD ±7), high dose methadone 94.3(SD ± 9) buprenorphine 95.7(SD ± 7). Alberta Infant motor score: Low dose methadone: 44.8(SD ±24), High dose methadone 38.1(SD ±24), buprenorphine 53.5 (SD ± 2). Suspect or abnormal neurological exam Low dose methadone: 19 (23%), high dose methadone 17 (21%), buprenorphine 7 (13%) Methadone group divided into low dose (<100mg / day) methadone (n = 84) or high dose (n = 81) during this study. Meta-analysis conducted as one group (methadone) compared to buprenorphine.	No adjusted results published.
Brogly 2017 USA	2006–2011 & 2015–2016	Retrospective cohort study	1020 477 methadone, 543 buprenorphine	Massachusetts Medicaid Analytic eXtract (MAX) dataset (2006-2011) and Boston dataset (2015–2016)	Inclusion: Age over 14yrs, delivered between 2006–2011 and had a Medicaid claim with opioid (or other drug) dependency. Exclusion: not specified	Prematurity: methadone 155 (32.9%), buprenorphine 99 (18.4%) Small for gestational age: methadone 61 (13%), buprenorphine 54 (10.9%) Length of offspring hospital admission: methadone 21.4days (SD ±15.7) buprenorphine 13.9days (SD ±12.6) Cesarean Section: methadone 179 (37.5%), buprenorphine 187 (34.3%)	Adjustments for maternal age, race/ethnicity, year of delivery, pre-natal selective serotine reuptake inhibitors or benzodiazepine before opioid substitution therapy. Buprenorphine compared to methadone. Prematurity: Risk ratio (RR) 0.53 (95% CI 0.39, 0.71) Small for gestational age: RR 1.13 (95% CI 0.77, 1.69) Length of hospital stay (days): −3.66 (-5.46, −1.87)
Colombini 2007 France	1998–2004	Prospective cohort study	21 9 methadone 13 buprenorphine	Single addiction center in Marseille France.	Inclusion: Offspring exposure to buprenorphine or methadone in pregnancy (mothers on established programs) Exclusion: not specified	Total birth weight of offspring: methadone 2826g (SD ± 461), buprenorphine 3093g (SD ± 342) Gestational age at birth: methadone 39.1weeks (SD ± 1.8), buprenorphine 39.9weeks (SD± 0.8) Treatment for NAS: methadone 9 (100%) and buprenorphine 13 (100%) Cesarean section: methadone 90 (0%), buprenorphine 2 (15%) Onset of NAS (range – hrs): methadone 6-24hrs, buprenorphine 24-168hrs. Not analyzed in meta-analysis as only range presented.	No adjusted results published.

(*Continued*)

Table 1. Continued.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Ebner 2007 Austria	Not specified	Prospective cohort study	36 22 methadone 14 buprenorphine	Single Specialist clinic in Austria	Inclusion: All neonates born to women who met criteria for opioid dependence during pregnancy (DSM-IV 304.0) and were enrolled in opioid maintenance therapy. Exclusion: Neonates born to mothers with alcohol and/or benzodiazepine codependency and twin pregnancies	Treatment for NAS: methadone 7(32%), buprenorphine 11 (74%) Time to develop NAS: methadone 57.5hrs (SD ± 37.5), buprenorphine 34.4hrs (SD ± 5.3) Birth weight, total length at birth and head circumference were reported to be not statistically significantly different between groups, due to lack of groups. Not including in meta-analysis due to lack of report of means or variation.	No adjusted results published.
Fischer 2005 Austria	2000–2002	Randomized control trial	18 9 methadone 9 buprenorphine	Single addiction clinic at the Medical University of Vienna, Austria	Inclusion: Opioid-dependent pregnant women diagnosis (DSM-IV = 304.0), older than 18 years, who presented at the addiction clinic of the Medical University Vienna. Informed consent and were willing to follow the protocol and to avoid use of illegal drugs whenever possible. Exclusion: outside recruitment window of 24 and 29 of pregnancy, positive drugs test for cocaine, benzodiazepine and severe somatic or other severe psychiatric diseases or a high-risk pregnancy.	Pre-term delivery (<37 weeks): methadone 3, buprenorphine 2, Treatment for NAS: 8 required treatments 3 in methadone group (50%), 5 in buprenorphine group (63%) Start of Treatment for NAS methadone 60hrs (SD11.3), buprenorphine 72hrs (SD 35.2) Cesarean section: methadone group 0, buprenorphine group 0 Dropouts of treatment: methadone 3, buprenorphine 1 Total birth weight of offspring mean: 2820g – not reported per group except for "no difference" therefore not analyzed.	No adjusted results published.
Gawronski 2014 USA	2010–2011	Retrospective cohort study	150 92 methadone 58 buprenorphine	Single center medical center Ohio (USA).	Inclusion: 18 years of age with a history of opioid dependence currently enrolled in a treatment program and stabilized on buprenorphine/naloxone or methadone Exclusion: not specified	Total birth weight of offspring: methadone 2905g (SD ± 567), buprenorphine 2904(SD ± 522) Total body length of offspring at birth: methadone 49cm (SD ± 4), buprenorphine 49 cm (SD ± 4) Head Circumference: methadone 33cm (SD ± 3), buprenorphine 33cm (SD ± 3) Preterm birth: methadone 22 (24%), buprenorphine 10 (17%). Gestational age at birth: methadone 37weeks (SD ± 2), buprenorphine 38weeks (SD ± 2) Treatment for NAS: methadone 74 (80%), buprenorphine 37 (64%) Time to NAS onset: methadone 2days (range 1-9), buprenorphine 2 days (range 1-6). No analyzed in meta-analysis due to unit of measure not being hours and only ranges presented. Length of offspring hospital admission: 10 days (SD ± 8), buprenorphine 9days (SD ± 6) Cesarean section: 20% - not analyzed in meta-analysis as no group break down.	No adjusted results published.

(*Continued*)

Table 1. Continued.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Jones 2005 USA	2000–2003	Randomized control trial	30 15 methadone 15 buprenorphine	Single center - Center for Addiction and Pregnancy, USA.	Inclusion: 21–40 years of age; estimated gestational age (EGA) by sonogram of 16–30 weeks; DSM-IV diagnosis of current opioid dependence; requesting maintenance pharmacotherapy; recent self-reported opioid use (more than 4 days of use in the past 7 days); and an opiate positive urine specimen at intake. Exclusion: a urine positive for undocumented methadone during intake; a current DSM-IV diagnosis of alcohol abuse or dependence; self-reported use of benzodiazepines (more than seven times per month and/or more than once a week); currently taking medication for another Axis I disorder; presence of a serious concurrent medical illness contraindicating study participation; diagnosis of pre-term labor; evidence of fetal malformation; positive HIV test; or positive sickle cell trait	Total birth weight of offspring: methadone 3001.8g(SE ± 120.7), buprenorphine 3530.4g(SE ± 162.7) Head circumference: methadone 33.2cm (SE ± 0.48), buprenorphine 34.9cm (SE ± 6.40) Gestation: methadone 38.8weeks (SE ± 0.56), buprenorphine 38.8 weeks (SE ± 0.76) Preterm births: methadone 1 (9.1%), buprenorphine 0(0.0%) Treatment for NAS: methadone 5(45%), buprenorphine 2 (20%) Duration of hospital stay: methadone 8.1days (SE ±0.78), buprenorphine 6.8 days (SE ± 0.86) Cesarean section: methadone 1 (9%), buprenorphine 1 (11%) 20 completed (11 methadone, 9 buprenorphine) Dropouts from treatment: methadone 4 (3 missed doses, 1 elective withdrawal), buprenorphine 6 (1 medical condition, 4 missed doses, 1 elective withdrawal).	No adjusted results published.
Jones 2010 Multi -center (USA + Austria)	2005–2008	Randomized control trial	175 89 methadone 86 buprenorphine	Multiple centers in North America and Europe	Inclusion: prescription of opioid replacement Exclusion: medical or other conditions contraindicating participation, pending legal action that might prevent their participation, disorders related to the use of benzodiazepines or alcohol, and birth planned outside the hospital at the study site.	Total birth weight of offspring: methadone 2878g (SE ± 66.3), buprenorphine 3092g (SE ±72.6) Total body length of offspring at birth: methadone 47.8cm (SE ± 0.5), buprenorphine 49.8cm (SE ± 0.5) Infant head circumference: methadone 33.0cm (SE ± 0.3), buprenorphine 33.8cm (SE ± 0.3) Prematurity: methadone 14(19%), buprenorphine 4(7%) Gestation age: methadone 37.9weeks (SE ± 0.3), buprenorphine 39.1weeks (SE ± 0.3) Treatment for NAS: methadone 41 (57%), buprenorphine 27 (47%) Duration of hospital stay methadone 17.5days (SE ± 1.5), buprenorphine 10.0days (SE ± 1.2) Fetal abnormalities: 1 case of dextrocardia reported (as surgical correction documented), no other reports but several other surgical procedures performed. Not analysis due to uncertain regarding incidence per group. Maternal adverse events: methadone 83 (93%) nonserious maternal events, and 14 (16%) serious. Buprenorphine 66 (77%) nonserious maternal events, and 8 (9%) serious. Cesarean section: Methadone 27 (37%) and Buprenorphine 17 (29%) Drop out from treatment: Methadone 16 (voluntary withdraw 10, involuntary 6) buprenorphine 28 (voluntary 26, involuntary 2)	No adjusted results published.

(*Continued*)

Table 1. Continued.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Kakko 2008 Sweden	1982 – 2006	Cohort study (Mixed – retrospective and prospective)	56 26 methadone 39 buprenorphine	Hospital ante-natal clinic in Stockholm, Sweden.	Inclusion: Prescription of methadone or prescription of buprenorphine and a DSM-IV criteria for drug dependency for at least 1 year. Exclusion: not specified	Intra-uterine deaths: methadone 0, buprenorphine 2 (5%) Gestational age at birth: methadone 38.6 weeks (SD ± 1.5), buprenorphine 39.5weeks (SD +- 2.0) Total birth weight of offspring: methadone 2941g (SD ± 483), buprenorphine 3250g (SD ± 528) Total body length at birth: methadone 47.6cm (SD ± 2.2), buprenorphine 48.4cm (SD ±2.5) Head Circumference: methadone 33.8cm (SD ± 1.5), buprenorphine 34.0cm (SD ± 1.4) Treatment for NAS: methadone 19 (52.8%), buprenorphine 7(14.9%) Length of offspring hospital admission: methadone 19.7days (SD ± 18.8) buprenorphine 9.4days (SD ± 8.4)	No adjusted results published.
Kaltenbach 2019 Multi-center (North America + Europe)	2005 – 2008	Randomized control trial	Randomized control trial	Multicentre in North America and Europe	Inclusion: Recruited in Jones et al., 2010, with same inclusion criteria. Exclusion: as per Jones et al., 2010.	Offspring development at 3-36months within normal range, no difference between buprenorphine and methadone.	No adjusted results published.
Konijnenberg 2015 Norway	2005 – 2007	Prospective Cohort study	66 24 methadone 11 buprenorphine 31 control	Multiple opioid maintenance therapy centers throughout Norway	All women in Norway during time period who gave informed consent.	No non adjusted results published.	Resulted adjusted for maternal education and employment. Executive function was lower in exposure neonatal compared to none exposed but mean group scores fell within the normal range of development. No difference demonstrated between methadone and buprenorphine.
Lacroix 2010 France	1998–2006	Prospective cohort study	135 45 methadone 90 buprenorphine	French maternity hospitals, maintenance therapy centers, and general practitioners involved in addiction care.	Inclusion: opioid replacement therapy. Exclusion Exclusion: multiple substitution therapies in the same pregnancy.	Total birth weight methadone 2,892g (SD± 506), buprenorphine 2,731g (SD ± 634) Length methadone 47.6cm (SD ± 2.5) buprenorphine 47.1cm (SD ± 3) Prematurity methadone 4 (9%), buprenorphine 16 (18%) Treatment for NAS methadone 20 (80%) buprenorphine 20 (23%) Onset of NAS: methadone 2.0days (SD ± 1.8), buprenorphine 2.8days (SD ±1.8) Maternal opioid use (Heroin): methadone 20 (44.4%), buprenorphine (16.7%) Malformations: methadone 2 offspring, buprenorphine 5 offspring Stillbirths: methadone 2 buprenorphine 1	Adjustments of requirement for treatment for NAS during concurrent heroin use and benzodiazepine. Requirement for NAS treatment controlled for heroin use: odd ratio (OR) 1.8 (95% CI 0.8–4.1). Requirement for NAS treatment controlled for benzodiazepines use: OR 1.49 (0.94–2.35)
Lejeune 2006 France	1998 – 1999	Prospective cohort case control study	259 100 methadone 159 buprenorphine	35 French perinatal centers and public hospitals	Inclusion: Receiving drug substitution that had started before or during this pregnancy Exclusion: not specified	Treatment for NAS: methadone 50 (49%), buprenorphine 78 (52%) Duration of hospital admission: methadone 28days, buprenorphine 16 days (not analysis as no presentation of distribution), Total birth weight of offspring (2822g), gestation (38.6weeks) or prematurity (14.6%) not analysis in meta-analysis as no per group analysis. Mean duration of treatment methadone 17days, buprenorphine 16 days (not analyzed as not presentation as distribution not reported).	No adjusted results published.

(*Continued*)

Table 1. Continued.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Myer 2016 USA	2000 - 2012	Retrospective cohort study	609 248 methadone 361 buprenorphine	Single addiction center in USA	Inclusion: All subjects in the center between 2000–2012 with exposure to methadone or buprenorphine Exclusion: Enrollment in the MOTHER study (Jones et al., 2010), not on opioid replacement, on opioid for other reason that addiction, delivered outside intuition or APGAR score of 0 (stillbirth)	Total birth weight of offspring: methadone 2899.7g (SD ± 583.1), buprenorphine 3143.3g (SD ± 578.9) Head circumference at birth: methadone 33.0cm (SD ± 2.0), buprenorphine 33.6cm (SD ± 2.1) Gestational age at birth: methadone 38.2weeks (SD ± 2.5), buprenorphine 39.2weeks (SD ± 2.2) Treatment for NAS: methadone 106 (42%), buprenorphine 82 (23%) Duration of treatment for NAS: methadone 133days (SD ± 83), buprenorphine 82days (SD ± 60) Length of offspring hospital admission (if EGA ≥ 37 weeks): methadone 5.6days (SD ± 2.8), buprenorphine 4.2days (SD ± 12.6) Stillbirths: methadone 4, buprenorphine 2 (1 mother in methadone group had twins, this is recorded as 1 still birth) Congenital deformity: methadone 1, buprenorphine 1 Total birth weight of offspring <5th Percentile: methadone 32 (13%), buprenorphine 40 (11%) – not analyzed under SGA in meta-analysis due to difference to standard definition of 10th percentile.	No adjusted results published.
Nechanska 2018 Norway	2004 –2013	Retrospective cohort study	235 99 methadone 97 buprenorphine	Entire Norwegian population	Inclusion: All patients prescribed of methadone or buprenorphine in Norway. Birth data from Medical Birth Registry of Norway (MBRN) and prescription from Norwegian Prescription Database (NorPD). Exclusion: not specified	Total birth weight of offspring: methadone 3268g (SD ± 603), buprenorphine 3333g (SD ± 437) Birth length: methadone 48.7com (SD ± 3.0), buprenorphine 49.3 (SD ± 2.0) Head circumference: methadone 34.4cm (SD ± 1.5), buprenorphine 34.7cm (SD ±1.6) Gestational age at birth: methadone 38.9weeks (SD ± 1.9), buprenorphine 39.2weeks (SD ± 2.4) Stillbirths: methadone <4, buprenorphine 0 (incidence recorded as less than 4 due to data-protection legislation) Preterm birth: methadone 9 (9.3%), buprenorphine 5 (5.2%) Small for gestational age at birth: methadone 10 (10.3%), buprenorphine 5 (5.2%) Treatment for NAS: methadone 55 (44.2–64.9) buprenorphine 51 (43.2-63.9) Cesarean section: methadone 23 (23.7%), buprenorphine 21 (23.7%)	Adjusted for maternal age, marital status, education, and tobacco smoking during pregnancy published. Buprenorphine compared to methadone, with methadone being the reference group. Preterm birth: Odds Ratio (OR) 0.73 (95% CI: 0.16 to 3.36) Small for gestational age: OR 0.83 (95% CI: 0.22 to 3.20) Treatment for NAS 0.94 (95% CI: 0.46–1.92) Linear regression performed for continuous dependant variables. Not analyzed as unable to pool published results. Gestational age age Beta-coefficient (β) 0.48 (95% CI: 0.29 to 1.25), Total Birth weight of offspring: β 83.1 (95% CI:-100.8 to 267.0), birth Length: β 0.47 (95% CI: 0.35 to 1.29), Head circumference: β 0.57 (95% CI: 0.04 to 1.18)

(*Continued*)

Table 1. Continued.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Nechanska 2018 Czech Republic	2000–2014	Retrospective cohort study	333 152 methadone 152 buprenorphine	Entire Czech Republic population	Inclusion: All patients in Czech Republic prescribed OAT as taken from National Register of Reproduction Health (NRRH) and National Register of Addiction Treatment (NRAT) datasets. Exclusion: not specified.	Total birth weight of offspring: methadone 3017g (SD ± 476), buprenorphine 3115g (SD ± 453) Small for gestational age at birth: methadone 19 (12.8%), buprenorphine 21 (13.8%) Birth length: methadone 48.1cm (SD ± 2.4), buprenorphine 48.6cm (SD ± 2.3) Head circumference at birth: methadone 33.8cm (SD ± 1.8) buprenorphine 34.0cm (SD ± 1.6) Gestational age at birth: methadone 38.3weeks (SD ± 2.6) buprenorphine 38.5weeks (SD ± 2.7) Stillbirth: methadone 4 (2.6%) buprenorphine 0 (0%) Preterm births: methadone 25 (16.9%) buprenorphine 25 (16.4%) Cesarean Section: methadone 23 (14.6%), buprenorphine 32 (22.1%) After adjustment for maternal age, marital status, education, and tobacco smoking during pregnancy	Adjusted for maternal age, marital status, education and tobacco smoking during pregnancy published. Buprenorphine compared to methadone, with methadone being the reference group. Preterm birth OR:0.92 (95% CI 0.48 to 1.74) Small for gestational age at birth OR 1.07 (95% CI: 0.52 to 2.21) Linear regression performed for continuous dependant variables. Not analyzed as unable to pool published results. Gestational age β: 0.05 (95% CI: 0.68 to 0.59), Total birth weight of offspring β 111.6 (95% CI: 10.5 to 233.6). Birth length: β 0.45 (95% CI: − 0.17 to 1.08), Head circumference at birth β 0.12 (95% CI: 0.41 to 0.65).
Norgaard 2015 Denmark	1997–2011	Retrospective cohort study	Total 364 197 methadone 167 buprenorphine	Entire Danish population	Inclusion: Danish population between 1997–2011 in the Danish Medical Birth Registry. Exclusion: not specified	Pre-term birth: methadone 41(21.2%), buprenorphine 25(15%) Small for gestational age at birth: methadone 7(3.6%), buprenorphine 4 (2.4) Treatment for NAS: methadone 106 (54.9%), buprenorphine 11 (6.6%) Congenital malformation: methadone 20 (10.4%), buprenorphine 14 (8.4%)	No adjusted results published.
Pritham 2013 USA	2005 – 2007	Retrospective cohort study	152 136 methadone 16 buprenorphine	Neonatal ICU, USA	Inclusion: Infants of mothers who received methadone or buprenorphine prescription in pregnancy and over 27 weeks' gestation Exclusion: None specified	Maternal use of opioids: methadone 128 (94%), buprenorphine 14 (93%). Gestational age at birth: methadone 37.6weeks (SD ± 2.1), buprenorphine 38.2weeks (SD ± 1.8) Birth weight: methadone 3132.7g (SD ± 2695.1), buprenorphine 3196.5g (SD ± 508.6) Head circumference: methadone 32.9cm (SD ± 2.6), buprenorphine 33.8cm (SD ±1.2) Small for gestation age at birth: methadone 14 (10.5%), buprenorphine 0 (0%) Treatment for NAS: methadone 115, 84.6%), buprenorphine 11 (68.8%) Age treatment started: methadone 1.84days (SD ±1.35), buprenorphine 1.87days (SD ±1.88) Length of hospital stay: methadone 21.3days (12.6), buprenorphine 13.7days (11.9)	Regression model used to examine methadone exposed offspring and length of stay not analyzed as no comparison to buprenorphine published.

(*Continued*)

Table 1. Continued.

Study	Period	Study type	Sample (N)	Setting	Inclusion/exclusion	Unadjusted results	Results
Tolia 2018 USA	2011 – 2014	Retrospective cohort study	3364 2202 methadone 1162 buprenorphine	Pediatrix Clinical Data from neonatal ICUs across the USA (241 centers)	Inclusion: singleton infants born ⩾36 weeks' gestation and diagnosed with NAS at or before 7 days of age. Exclusion: not specified	Total birth weight of offspring: methadone 3047g (SD ±474) buprenorphine 3000g (SD ± 467) Gestational age at birth: methadone median 39weeks (range 38-39), buprenorphine median 39weeks (range 37-39) – no meta-analysis due to medium / range provided not standard deviation. Small for gestational age at birth: methadone 400 (18%), buprenorphine 158 (14%) Cesarean section: methadone 859 (40%), buprenorphine 404 (36%)	Adjusted results for maternal age, parity, race and ethnicity, prenatal care, smoking status, use of antidepressants, use of benzodiazepines, gestational age, small for gestational age status, cesarean delivery, sex, out born status, type of pharmacotherapy, breast milk use, year and controlled for center with robust sandwich variances) Not analyzed as unable to pool published results. Small for gestational age at birth: Hazard Ratio (HR) 0.87 (0.78, 0.97, 95% CI 0.78, 0.97). Cesarean delivery HR 0.98 (0.90, 1, 1.07)
Whitham 2010 Australia	2002 - 2006	Open-label non-randomized flexible-dosing longitudinal study	52 22 methadone 30 buprenorphine	2 specialist drug and alcohol antenatal clinics Adelaide, South Australia.	Inclusion: prescription of methadone o buprenorphine and <28 weeks gestational and mothers aged between 16-40yrs. Exclusion: medical illness requiring medication that interacted with the maintenance drug or was known to affect pregnancy outcomes; alcohol consumption greater than seven standard drinks per week; multiple pregnancy; any signs of congenital fetal malformations on admission; participation in another clinical research project that interfered with the present study.	Total birth weight of offspring: methadone 2749.09g (SD ± 484.32), buprenorphine 3055.52 (SD ±511.65) Birth length: methadone 46.52cm (SD ±3.21), buprenorphine 47.93 (SD ± 2.54) Head circumference: methadone 32.65cm (SD ± 1.34), buprenorphine 33.7cm (SD ± 1.81) Gestational age at birth: methadone 38.09weeks (SD ± 1.95, buprenorphine 38.73weeks (SD ± 1.95) NAS treatment required: methadone 11(50%), buprenorphine 14 (47%)	Adjustment for age, family income, Marijuana use, and adjustment used for visual studies (not analyzed as not relevant outcome for this meta-analysis).
Wiegand 2015 USA	2011–2013	Retrospective cohort study	62 patients (31 methadone, 31 buprenorphine + naloxone)	Single addiction center Northern Carolina Chapel Hill, USA.	Inclusion: prescription of opioid replacement Exclusion: treatment started less than 30day before delivery, delivery at an outside hospital, multiple gestations, intrauterine fetal demise or still-birth, or an anomalous fetus or new-born and multiple births.	Treatment for NAS: methadone 16 (51%), buprenorphine 8 (21%) Duration of NAS: methadone 11.4days (SD ± 3.4), buprenorphine 10.6 (SD ± 3.1) Head Circumference at birth: methadone 32.9 (SD ± 2.5), buprenorphine 34.4 (SD ± 1.4) Total birth weight of offspring: methadone 2885.9 (SD ± 691.2), buprenorphine 3174g (SD ± 532.8) Total length of offspring at birth: methadone 47.9cm (SD ± 4.0), buprenorphine 50.1 (SD ± 2.5) Preterm: methadone 5(16.1%), buprenorphine 1(19.4%) Length of hospital admission: methadone 9.8days (SD ± 7.4), buprenorphine 5.7 (SD ± 5.0) Cesarean Section: methadone 8 (25.8%), buprenorphine 7 (22.6%)	Adjustment for gestational age and maternal indication for opiates. Buprenorphine compared to methadone, with methadone being the reference group. Treatment for NAS: OR 2.55 (95% CI: 1.31–4.98)

additional papers were added following screening of citations in previously published papers in the field (Colombini et al., 2008; Gawronski et al., 2014; Konijnenberg & Melinder, 2015; Nørgaard et al., 2015). 408 studies were screened by title and abstract, 129 of which were selected as potentially includible and evaluated as full text articles. 20 papers met criteria for inclusion in the meta-analysis (Table 1). Two papers were included in the results for development outcomes only (Kaltenbach et al., 2012; Konijnenberg & Melinder, 2015), as birth and maternal outcomes were reported from these populations in other papers in this meta-analysis. The CONSORT flow diagram is shown in Figure 1.

The 20 studies in this meta-analysis included 7251 patients (methadone n = 4146, buprenorphine n = 3105), in 4 RCTs and 16 cohort studies. The location of the studies was Europe (8), North America (10) and Oceania (2). Of the 16 cohort studies, 8 studies provided adjusted results for a total of 4 outcomes (small for gestational age, prematurity, duration of hospital admission, and NAS treatment). Characteristics of each study are given in Table 1 and results of pooled estimates for both adjusted (where available) and unadjusted analyses for cohort studies are presented in Supplementary Table 7.

The risk of bias was high for all the randomized trials (4/4). The median (IQR) Newcastle Ottawa Scale was 7.5 (6-9) for cohort studies (Supplementary Tables 5 and 6). A funnel plot was produced for outcomes with more than 10 studies, and there was no apparent asymmetry in these plots (Supplementary Figure 1).

Neonatal growth

Birthweight was reported in 14 studies (12 cohort, 2 RCTs). The weighted mean difference in offspring birth weight was 184 g (95% CI: 121–247 g) in cohort studies and 343 g (95% CI: 40–645 g) in RCTs favoring buprenorphine (Figure 2). One paper (Pritham et al., 2012), reported a standard deviation of 2695 g (4 times greater than other studies). When this study was excluded from the results, the weighted mean difference was 186 g (95% CI: 122–250 g) in cohort studies. Length at birth was measured in 9 studies (7 cohort, 2 RCTs), and was 0.65 cm (95% CI: 0.31 cm-0.98 cm) greater in the cohort studies and 2.28 cm (95% CI: 1.06–3.49 cm) greater

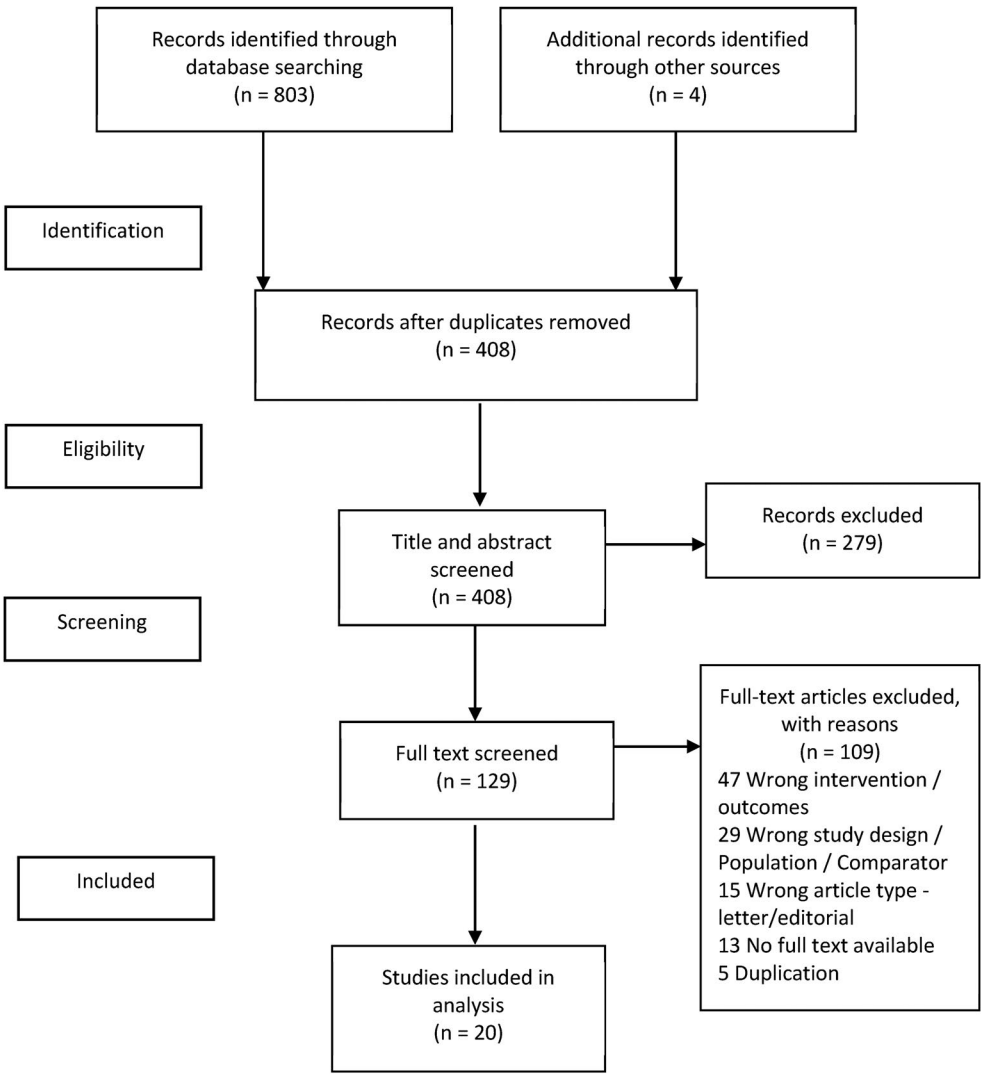

Figure 1. CONSORT flow diagram of studies included in analysis.

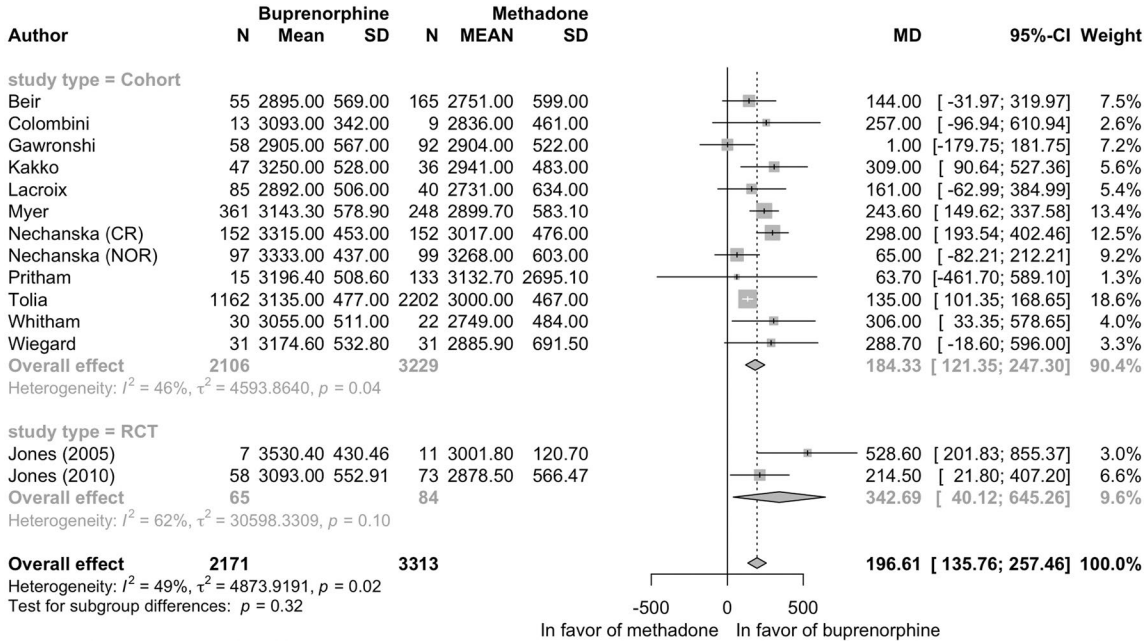

Figure 2. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and weighted mean difference in offspring birth weight (grams).

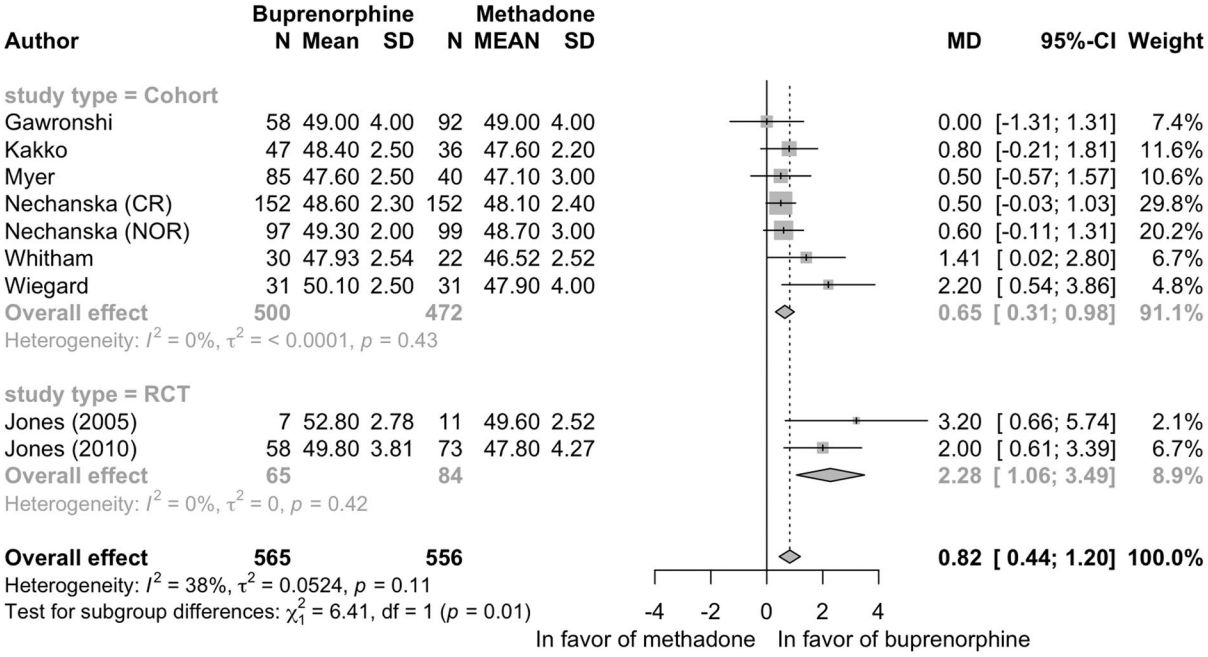

Figure 3. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and weighted mean difference in offspring total body length (centimetres).

in RCTs with buprenorphine compared to methadone (Figure 3). Head circumference was measured in 9 studies (7 cohort, 2 RCTs). Buprenorphine was associated with a 0.42 cm (95% CI: 0.20–0.64 cm) increase in head circumference in the cohort studies, and no change in RCTs (weighted mean difference of 0.80 cm (95% CI: −0.03 to 1.63 cm). None of the cohort studies reporting birth weight or length at birth provided adjusted estimates. Small for gestational age (SGA) was investigated in 5 studies (all cohort studies). The risk ratio for SGA was 0.76 (95% CI: 0.66–0.88), in favor of buprenorphine. When this analysis was restricted to the three studies where the outcome was adjusted for confounding, or when both adjusted and unadjusted estimates were pooled, the risk ratio was no longer significant (Supplementary Table 7).

Gestational age

Gestation was measured in 11 studies (9 cohort, 2 RCTs). Buprenorphine was associated with an increase in gestational age of 0.55 weeks (95% CI: 0.25–0.84 weeks) in cohort studies (unadjusted estimates only), but no difference in RCTs (weighted mean difference of 0.9 weeks (95% CI: −0.13 to

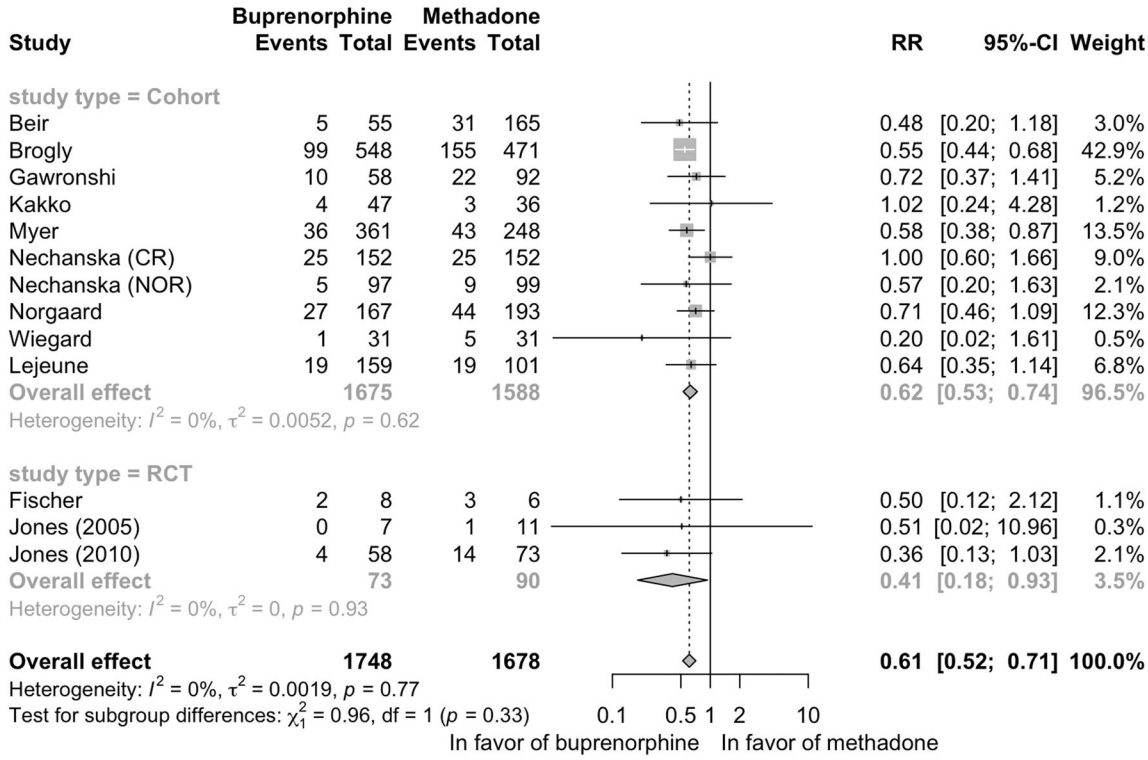

Figure 4. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and risk ratio for prematurity.

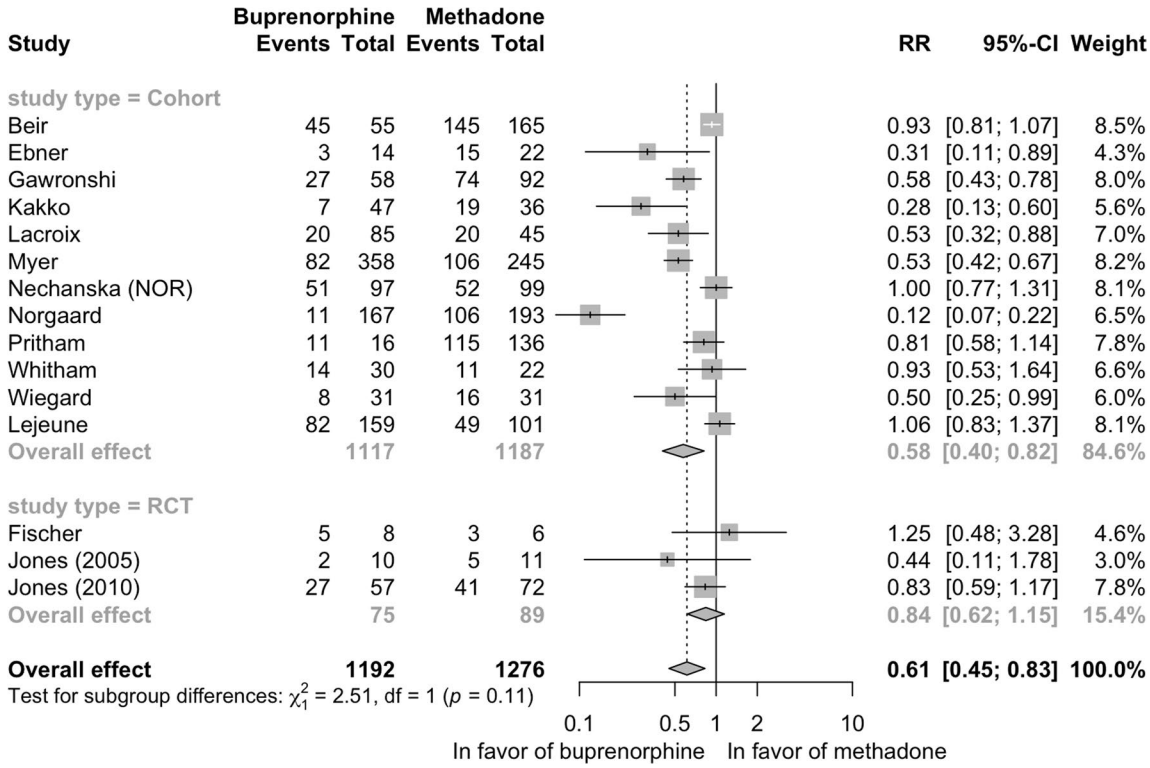

Figure 5. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and risk ratio for NAS treatment.

1.92). No cohort studies provided adjusted estimates for this outcome. Prematurity was reported in 12 studies (9 cohort, 3 RCTs). Buprenorphine treatment was associated with a reduced risk of prematurity in both cohort (RR 0.62, 95% CI: 0.53–0.74) and RCTs (RR 0.41, 95% CI: 0.18–0.93) - Figure 4.

Neonatal abstinence syndrome

15 studies (12 cohort, 3 RCTs) reporting treatment for NAS showed a reduction in the relative risk of requiring treatment in mothers receiving buprenorphine in cohort studies

(RR 0.58, 95% CI: 0.40–0.82), but not RCTs (RR 0.84, 95% CI 0.62–1.15) - Figure 5. When the analysis of cohort studies was restricted to those providing adjusted estimates (3 studies) (Lacroix et al., 2011; Nechanská et al., 2018; Wiegand et al., 2015), this difference was no longer statistically significant (Supplementary Table 7). The duration of hospital admission was measured in 9 studies (7 cohort and 2 RCTs). Buprenorphine was associated with a reduction of 6.84 days (95% CI: −11.37 days – −2.32 days) in cohort studies, and no change in RCTs (-4.21 days, 95% CI: −10.28–1.85). Only one study (Brogly et al., 2018) provided adjusted estimates for this outcome (mean difference −3.66 days, 95% CI: −5.46 days - −1.87 days)

Congenital anomalies, stillbirths and offspring deaths

Three cohort studies (all reporting unadjusted outcomes) reported congenital anomalies (486 methadone-exposed and 618 buprenorphine-exposed offspring). There were 23 (4.7%) malformations in methadone- exposed neonates and 20 (3.2%) malformations in buprenorphine-exposed neonates. When results where pooled, there was no difference between groups (RR 0.85, 95% CI: 0.47–1.54). The malformations reported in the methadone group included: poly-malformation, absent hand, and dextrocardia. In the buprenorphine group malformations reported included: tragus appendix, nasal septum deviation, short neck, gastroschisis, facial abnormalities, microcephaly, and cleft palate. One study reported a malformation rate of 39,934 (4.2%) in a reference group of non-opioid users (n = 945,569) (Nørgaard et al., 2015).

Seven studies reported stillbirths (596 methadone-exposed and 759 buprenorphine-exposed offspring) with the relative risk of stillbirth lower in cohort studies (RR 0.38, 95% CI: 0.12-1.20), however the confidence intervals included unity. There was one stillbirth (methadone group) in the three RCTs (86 buprenorphine exposed, 89 methadone exposed), and a relative risk could not be calculated. No offspring deaths were reported in either cohort or RCTs.

Childhood development

Three studies reported development outcomes, however due to heterogeneity in outcome measures these results could not be pooled. Bier et al. (2015) investigated development at 4 months with the Bayley Mental Developmental Index (MDI) and the Alberta Infant Motor Scale (AIMS). There were no significant differences in Bayley MDI scores between methadone (high and low dose groups) and buprenorphine. AIMS scores were different between groups with buprenorphine-exposed offspring having higher scores, compared to methadone (low and high dose groups). The proportion of infants with suspected or abnormal neurological examination was not significant between low dose methadone (n = 19 [23%]), high dose methadone (n = 17 [21%]) and buprenorphine-exposed groups (n = 7 [13%]). Whitham et al. (2010) measured visual evoked protentional at 4-months old, infants exposed to methadone (n = 22) had prolonged latency compared to controls and buprenorphine-exposed offspring (n = 30). Kaltenbach et al. (2018) followed up participants (n = 96, methadone n = 52, buprenorphine n = 44) of the 2010 Jones et al. trial. It was observed that these offspring had normal development at 36 months.

Maternal outcomes

One RCT (175 patients) systematically measured and documented maternal outcomes (Jones et al., 2010). There were 14 (16%) serious adverse events and 83 (93%) non-serious adverse events in the methadone arm, and 8 (9%) serious adverse events, and 66 (77%) non-serious events in the buprenorphine arm. Three RCTs reported retention rates (Fischer et al., 2006; Jones et al., 2005, 2010). In the methadone arms, 23/113 (20%) mothers dropped out, while in the buprenorphine arms 35/110 (32%) dropped out of the studies. The relative risk of drop-out from treatment was 1.60 (95% CI: 1.00–2.55) when taking buprenorphine compared with methadone. Two cohort studies reported measures of additional opioid use throughout pregnancy (unadjusted analyses). Lacroix reported that 15/90 (17%) of women used heroin in the buprenorphine group versus 20/45 (44%) in the methadone group. Pritham et al. (2012) reported 14/16 (88%) patients using additional opioids in the buprenorphine group, and 128/136 patients (94%) of patients in the methadone group. When the results of these two studies were pooled, there was no difference between groups (RR 0.61, 95% CI: 0.25, 1.49).

The rate of cesarean section was measured in 11 studies (8 cohort studies and 3 RCTs). Buprenorphine treatment was associated with a reduction in the rate of cesarean sections in cohort studies (unadjusted analyses), relative risk 0.90 (95% CI: 0.84–0.98). There was no difference in RCTs (RR 0.84 (95% CI: 0.52; 1.36). No maternal deaths were reported in the studies.

Discussion

This meta-analysis shows that offspring who are exposed to buprenorphine, compared to methadone have greater birthweight, longer length at birth, and lower risk of prematurity in both RCTs and cohort studies. In RCTs, there was a greater risk of maternal adverse events with methadone, but higher drop-out rates with buprenorphine. Analysis of the cohort studies demonstrated greater head circumference, longer gestation, lower requirements for NAS treatment, shorter neonatal hospital stay, and reduced risk for cesarean section, however, these differences were not observed in the RCTs. There was no difference in risk of congenital malformations, small for gestational age, stillbirths or additional maternal opioid use in cohort studies, with insufficient data to analyze these outcomes in RCTs. Longer term childhood outcomes had insufficient data to make robust conclusions. Similarly adjusted estimates accounting for potential confounders were only available in half of the cohort studies and for only four outcomes. Of these only duration of hospital admission remained statistically

significant in adjusted analyses. Collectively this data would suggest that buprenorphine may be beneficial compared to methadone, however, larger more robust studies are required.

This meta-analysis updates existing literature to include all available evidence from both RCTs and observational cohort studies comparing methadone and buprenorphine for opioid using mothers. Our findings confirm the results of previous meta-analyses regarding beneficial effects of buprenorphine on growth. Three smaller meta-analyses (n = 271 to 2146) have been published on this topic (Brogly et al., 2014; Minozzi et al., 2020; Zedler et al., 2016). Two meta-analyses (Brogly et al., 2014; Zedler et al., 2016) included RCTs and observational studies, while a third meta-analysis (Minozzi et al., 2020) was conducted including only RCTs (3 studies (Fischer et al., 2006; Jones et al., 2005, 2010) comparing methadone to buprenorphine). The meta-analysis of RCTs and observational studies by Brogly et al. (2014) reported an association with lower NAS treatment risk and treatment duration as well as shorter hospital stay in neonates exposed to buprenorphine compared with methadone, in a sample of 1370 patients. Buprenorphine was associated with greater mean gestational age, higher birthweight, longer length at birth, and larger head circumference at birth, and reduced illicit maternal opioid use near delivery. Adjustment for bias, including confounding by indication, attenuated these findings but there was still clinically and statically significant improvement in the buprenorphine group. In 2016 a meta-analysis including 3 RCTs and 15 cohort studies (2146 patients) reported similar results with buprenorphine exposed offspring having lower risk of preterm birth, greater birth weight, and larger head circumference compared with methadone exposed offspring but did not adjust for confounding (Zedler et al., 2016). A 2020 Cochrane review by Minozzi et al. included four randomized controlled trials (271 patients), three of which directly compared buprenorphine to methadone, this analysis found no significant differences for maternal or neonatal outcomes between treatments. Evidence was considered of moderate or low quality due to small sample sizes and high drop-out rates as well as a lack of reporting of smoking status and inconsistencies in results. Long-term development outcomes were not included in these meta-analyses.

In our meta-analysis, we estimate a weighted mean increase in birthweight of 184 grams in cohort studies and 343 grams in RCTs in buprenorphine-exposed, compared to methadone-exposed offspring. This compares favorably to the 174 grams reduction in birthweight seen in offspring of women who smoke during pregnancy to those who do not smoke cigarettes (Delpisheh et al., 2006). The magnitude of improvement should be interpreted with caution due to possibilities of bias, (Brogly et al., 2015) especially as our meta-analysis was unable to control for differences in smoking rates between groups.

There are several strengths to this study. We included both cohort and RCTs, used comprehensive search terms, and reported a wide range of maternal and offspring outcomes including that of longer-term childhood development. We report pooled results, separately for both RCTs and observational studies, reflecting what we believe is the totality of research directly comparing methadone and buprenorphine in pregnancy. The main limitation of this study is that we did not adjust for confounding by indication in the included observational studies, and this may predispose to bias. It is believed that higher-risk opioid-using mothers may preferentially be treated with methadone rather than other agents (Brogly et al., 2016). Higher risk patients are expected to have neonates with worse outcomes due to differences in opioid substitution use as well as other drug use, increased maternal stress and smoking rates.

When correction for confounding by indication was accounted for in a previous meta-analysis, indices of growth differences were no longer significant, but the level of NAS treatment remained reduced (Brogly et al., 2014). A further meta-analysis by Zedler et al. (2016) did not correct for confounding arguing that any corrections were based on largely "subjective" (Joyce et al., 2016) and potentially severe assumptions for key parameter values. Similarly, to Zedler and colleagues, we did not correct for bias in this study as it is not clear to what direction or extent bias can exist and we were concerned that the introduction of a correction factor biased on prior beliefs might introduce further bias. It is also possible that any existing bias, due to differences in prescription practices, training, and familiarization may change over time. Whilst we agree that ideally correction for confounding would be performed, this methodology requires further development before being widely implemented. We have reported analyses using adjusted estimates where these are available, though we accept that these are reported in only half of the included cohort studies, and for only a minority of outcomes.

A further limitation of this study was the significant risk of bias due to high drop-out rates and lack of a priori published protocols in randomized trials. These limitations are significant but expected when investigating the topics of opioid replacement in pregnancy due to the population studied and side-effects of treatment programs.

This meta-analysis has highlighted that further research is required into longer-term childhood development, specifically looking at any differences between drug groups and formulations. Few studies have investigated developmental outcomes, and meta-analysis has not been performed. Opioid replacement (buprenorphine or methadone) compared to no opioid replacement is negatively associated with a range of offspring developmental outcomes but differences between specific opioids have not been fully investigated (Andersen et al., 2020; Murawski et al., 2015; Nygaard et al., 2015, 2017; Oei, 2018; Oei et al., 2017; Ross et al., 2015). The measurement of developmental effects is complicated by a multitude of factors including type and timing of testing, and preexisting differences between groups, as well as difficulties in recruitment of participants. Development concerns are increased in the first year of life (Whitham et al., 2010), only to recede in later years (Kaltenbach et al., 2018; Whitham et al., 2015). Different drug formulations such as buprenorphine-naloxone in combination may have additional advantages such as decreasing the risk of diversion and misuse. A recent meta-analysis of buprenorphine combined with naloxone compared with other opioid replacement

regimes (methadone, buprenorphine, or long-acting opioids) showed no difference between groups but did not include any longer term follow up (Link et al., 2020). Further randomized controlled trials including larger populations, and with less loss to follow-up is aspirational but may not be feasible. Larger cohort studies using routinely collected healthcare data allow for larger sample sizes compared with RCTs but are limited by their observational nature and potential confounding. Further efforts to control for confounding may be achieved by the collection of detailed data on demographics, social factors, other determinants of health, and other drug use, including smoking and alcohol.

This meta-analysis shows that buprenorphine is associated with improvements in growth when compared to methadone. The priority for opioid replacement care programs remains the delivery of non-judgmental support, addressing of individual needs and maintenance of stability of treatment.

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Drs Kinsella, Capel, Halliday, Shaw and Kearns report no conflicts of interest. Scott Nelson has participated in Advisory Boards and received consultancy or speakers' fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, MSD, Roche Diagnostics, and The Fertility Partnership.

Author contributions

Michael Kinsella, Rachel Kearns and Scott Nelson developed the original concept of the study as well as lead data-extraction and writing of manuscript. Lucy Halliday provided data-extraction quality control and arbitrated disputes in screening. Yasmin Capel performed screening of all papers along with Michael Kinsella. Rachel Kearns obtained the funding for this work, supported design of study, supervised writing and review of the manuscript. Scott Nelson and Martin Shaw supported design of study and critically reviewing and revising the manuscript for important intellectual content.

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Statement of ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

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Data availability statement

All data used in the preparation of this manuscript is derived from published materials and can be accessed via literature search as outlined in methods and supplemental material.

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