Increasing rates of maternal opioid use during pregnancy and neonatal withdrawal, termed neonatal abstinence syndrome (NAS), are public health concerns. Prenatal buprenorphine maintenance treatment (BMT) versus methadone maintenance treatment (MMT) may improve neonatal outcomes, but associations vary. To summarize evidence, we used a random-effects meta-analysis model and estimated summary measures of BMT versus MMT on several outcomes. Sensitivity analyses evaluated confounding, publication bias, and heterogeneity. Subjects were 515 neonates whose mothers received BMT and 855 neonates whose mothers received MMT and who were born from 1996 to 2012 and who were included in 12 studies. The unadjusted NAS treatment risk was lower (risk ratio = 0.90, 95% confidence interval (CI): 0.81, 0.98) and mean length of hospital stay shorter (−7.23 days, 95% CI: −10.64, −3.83) in BMT-exposed versus MMT-exposed neonates. In treated neonates, NAS treatment duration was shorter (−8.46 days, 95% CI: −14.48, −2.44) and morphine dose lower (−3.60 mg, 95% CI: −7.26, 0.07) in those exposed to BMT. BMT-exposed neonates had higher mean gestational age and greater weight, length, and head circumference at birth. Fewer women treated with BMT used illicit opioids near delivery (risk ratio = 0.44, 95% CI: 0.28, 0.70). Simulations suggested that confounding by indication could account for some of the observed differences. Prenatal BMT versus MMT may improve neonatal outcomes, but bias may contribute to this protective association. Further evidence is needed to guide treatment choices.

buprenorphine; infant; methadone; neonatal abstinence syndrome; newborn; pregnancy

Abbreviations: BMT, buprenorphine maintenance treatment; CI, confidence interval; MMT, methadone maintenance treatment; NAS, neonatal abstinence syndrome; RCT, randomized controlled trial.
results have varied, sample sizes have been small, and few studies have controlled for possible confounding by indication. In the United States, BMT is provided in office-based settings by licensed physicians, and women fill prescriptions and take BMT on their own. In contrast, women prescribed MMT must attend dispensing clinics daily for observed MMT dosing. Thus, the severity of maternal opioid dependence and social conditions influence clinical prescribing, with BMT typically being used to treat more stable opioid-dependent pregnant women who do not need the structure of observed daily dosing (12, 14, 17–19). Potential confounding by indication can occur in assessing the comparative safety of prenatal BMT versus MMT because maternal characteristics that might influence the choice of prenatal treatment (BMT vs. MMT) likely also affect neonatal outcomes.

The goals of this study were to conduct a systematic review of the published literature, to perform a meta-analysis of the association of prenatal BMT versus MMT exposure on the neonate, and to explore potential sources of heterogeneity and bias among studies.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (20). Computerized searches were performed in PubMed, the Cochrane Central Register of Controlled Trials, and the Cochrane database. We included publications from January 2000 (buprenorphine was approved for use in adults by the Food and Drug Administration in 2002) through October 2013. To identify studies comparing human neonatal exposures to BMT and MMT, we used combinations of the following medical subject headings and keywords: buprenorphine, methadone, opioid agonist therapy, pregnancy, infant, and neonatal abstinence syndrome. References of retrieved articles were also manually searched. Two investigators (S.B.B. and H.M.D.) independently identified studies and extracted information on study design, results, and potential bias. Our study outcomes were based on those reported in the literature. Binary outcomes were pharmacological treatment for NAS, preterm birth (<37 weeks’ gestation), and illicit maternal opioid use detected late in pregnancy. The definition of the latter variable differed across studies, with some reporting urine screening results from the third trimester, during the last 4 weeks of pregnancy, late in pregnancy, or at delivery. Continuous outcomes were the mean difference in length of hospital stay, length of NAS treatment, amount of morphine used to treat NAS, gestational age at birth, and neonatal birth weight, body length, and head circumference. Study results abstracted included the number of subjects, proportions, means, and standard deviations. The original study authors were contacted to address potential data errors in 2 of the original articles (12, 16). Most studies identified were small and did not adjust for potential confounding. Thus, in our quality assessment of the published literature, we excluded 1 study because of study design limitations (18) (further discussed in results).

We used an inverse variance–weighted random-effects model to calculate summary estimates and account for variance within and between studies (21). All identified studies estimated the odds ratio of NAS treatment in BMT- versus MMT-exposed neonates; however, we calculated the summary risk ratio because the odds ratio overestimates the risk ratio given the high risk of NAS treatment (22). We calculated summary mean differences for our continuous outcomes. Most studies reported crude estimates, and these were included in our meta-analysis. As part of the design strategy of 1 RCT (11), the primary analysis was adjusted for study site, and these results were included in our meta-analysis. One cohort study provided unadjusted results and results adjusted for heroin use late in pregnancy (14); however, we did not include the adjusted results because failure of agonist therapy to prevent prenatal drug use is not a confounder but rather part of the total effect of agonist therapy on the neonate (23).

We conducted sensitivity analyses to assess heterogeneity, publication bias, and confounding. Summary estimates were calculated separately by study design (RCT vs. cohort study) to examine consistency with our overall estimates. We also performed meta-regression, adjusting for study design (RCT vs. cohort). Although the number of comparative studies included was small, we recalculated summary estimates excluding 1 study at a time to see if the summary estimates were heavily influenced by a particular study. Heterogeneity among studies was statistically assessed with the Cochran Q statistic (24) and Galbraith plots and was quantified by the $I^2$ statistic (25). Publication bias was visually examined using funnel plots (26).

We explored potential unmeasured confounding by indication in our meta-analysis using the bias formulas of VanderWeele and Arah (27). For our continuous outcomes, the confounding effect in the BMT group ($MD_{\text{confounder, BMT}}$) was defined as the mean difference in a particular study outcome of mother-neonate pairs assigned to BMT because of indication ($X_2$) and those assigned to BMT for a reason other than indication ($X_1$), such as random assignment in an RCT. Likewise, the confounding effect in the MMT group ($MD_{\text{confounder, MMT}}$) was defined as the difference of a particular study outcome in mother-neonate pairs assigned to MMT because of indication ($X_4$) and those assigned to MMT for a reason other than indication ($X_3$). The adjusted mean difference ($MD_{\text{adjusted}}$) in neonatal outcomes in the BMT versus MMT groups was calculated as

$$MD_{\text{adjusted}} = MD_{\text{unadjusted}} - [(X_2 - X_1) p_1 - (X_4 - X_3) p_0],$$

which can be rewritten as

$$MD_{\text{adjusted}} = MD_{\text{unadjusted}} - (MD_{\text{confounder, BMT}} p_1 - MD_{\text{confounder, MMT}} p_0),$$

where $MD_{\text{unadjusted}}$ is the unadjusted mean difference in neonatal outcomes estimated in our meta-analysis, and $p_1$ and $p_0$ are the prevalence of receiving BMT and MMT due to confounding by indication, respectively.

Cohort studies have consistently suggested that confounding by indication would likely occur via use of BMT versus MMT in more stable opioid-dependent pregnant women (12, 14, 16, 17, 19). Therefore, we assumed that confounding by indication would exacerbate poor outcomes in the MMT group.
Table 1. Studies of Prenatal Buprenorphine Maintenance Treatment Versus Methadone Maintenance Treatment and Neonatal Outcomes, Births From 1982 to 2012

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>Participants</th>
<th>Location</th>
<th>Years of Birth</th>
<th>Maternal Treatment Delivery</th>
<th>NAS Assessment</th>
<th>NAS Treatment</th>
<th>Potential Sources of Bias</th>
<th>Analytical Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones, 2010 (11)</td>
<td>RCT</td>
<td>175 Mother-neonate pairs</td>
<td>Six sites in the United States, Canada, and Austria</td>
<td>2005–2008</td>
<td>Randomized; women attended daily dispensing study clinic for blinded active therapy (BMT or MMT) plus blinded placebo</td>
<td>Modified Finnegan scale</td>
<td>Morphine</td>
<td>Rates of study dropout (for BMT group, 33%; for MMT group, 18%); lifetime use of heroin (for BMT group, 25.4 months; for MMT group, 45.7 months)</td>
<td>Primary per-protocol analysis of women who remained in study adjusted for study site; supplementary analysis adjusted for number of days of BMT or MMT, cigarette and SSRI use at study enrollment, percent of urine tests positive for cocaine during pregnancy, number of prenatal visits at enrollment, and gestational age at delivery</td>
</tr>
<tr>
<td>Binder, 2008 (28)</td>
<td>RCT</td>
<td>147 Mother-neonate pairs at a perinatal care unit</td>
<td>Prague, Czech Republic</td>
<td>2002–2007</td>
<td>BMT, MMT, or heroin; details of treatment allocation and dispensing not provided</td>
<td>Finnegan scale</td>
<td>Diluted tincture of opium</td>
<td>Study dropout (n = 30); randomization details not provided</td>
<td>Unadjusted and per-protocol analysis of women who remained in study</td>
</tr>
<tr>
<td>Fischer, 2006 (29)</td>
<td>RCT</td>
<td>18 Mother-neonate pairs at an addiction clinic</td>
<td>Vienna, Austria</td>
<td>2000–2002</td>
<td>Randomized; women attended daily dispensing study clinic for blinded active therapy (BMT or MMT) or blinded placebo</td>
<td>Finnegan scale</td>
<td>Morphine hydrochloride</td>
<td>Rates of study dropout (for BMT group, 11%; for MMT group, 33%); median numbers of positive urine samples for illicit opioids (for BMT group, 35.26; for MMT group, 4.35)</td>
<td>Unadjusted and per-protocol analysis of women who remained in study</td>
</tr>
<tr>
<td>Jones, 2005 (13)</td>
<td>RCT</td>
<td>30 Mother-neonate pairs at a multidisciplinary treatment program</td>
<td>Baltimore, Maryland</td>
<td>2000–2003</td>
<td>Randomized; women attended a daily dispensing clinic for blinded active therapy (BMT or MMT) or blinded placebo</td>
<td>Modified Finnegan scale</td>
<td>Morphine solution</td>
<td>Rates of study dropout (for BMT group, 40%; for MMT group, 27%)</td>
<td>Unadjusted and per-protocol analysis of women who remained in study</td>
</tr>
<tr>
<td>Wachman, 2013 (30)</td>
<td>Prospective multisite cohort</td>
<td>86 Mother-neonate pairs at tertiary and community care centers</td>
<td>Massachusetts and Maine</td>
<td>2011–2012</td>
<td>Patient/provider selected therapy; BMT provided through prescription and self-administered; MMT daily dosing at licensed clinic</td>
<td>Modified Finnegan scale</td>
<td>Morphine or methadone (first-line); phenobarbital or clonazepam (second-line)</td>
<td>Differences in neonatal treatment; possible prenatal agonist therapy use by institution</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Welle-Strand, 2013 (15)</td>
<td>Cohort</td>
<td>139 Mother-neonate pairs receiving OMT</td>
<td>Norway</td>
<td>1996–2009</td>
<td>BMT first-line therapy since 2005; BMT or MMT determined through OMT program and provided by general practitioner following stabilization at OMT program regional center</td>
<td>Modified Finnegan scale and Lipsitz scale</td>
<td>Phenobarbital; opium tincture; morphine sulfate</td>
<td>Median duration of opioid use (for BMT group, 7 years; for MMT group, 8 years); changes in data collection over calendar time; BMT as first-line therapy since 2005; infants born at 18 hospitals</td>
<td>Unadjusted and adjusted for maternal age, years of opioid dependency before treatment, dose of BMT or MMT at delivery, cigarette use, and other drug use 1 month before pregnancy confirmation</td>
</tr>
</tbody>
</table>

Table continues
<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>Participants</th>
<th>Location</th>
<th>Years of Birth</th>
<th>Maternal Treatment Delivery</th>
<th>NAS Assessment</th>
<th>NAS Treatment</th>
<th>Potential Sources of Bias</th>
<th>Analytical Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritham, 2012 (16)</td>
<td>Retrospective cohort</td>
<td>152 Mother-neonate pairs delivered at a medical center and community hospital</td>
<td>Maine</td>
<td>2005–2007</td>
<td>Patient/provider selected therapy; BMT provided through prescription and self-administered; MMT daily dosing at licensed clinic</td>
<td>Not provided</td>
<td>Phenobarbital (first-line); diluted tincture of opium (second-line)</td>
<td>Rates of marijuana use during pregnancy (for BMT group, 18.2%; for MMT group, 42.7%); limited information on confounders</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Wachman, 2011 (10)</td>
<td>Retrospective chart review</td>
<td>273 Mother-neonate pairs delivered at Boston Medical Center</td>
<td>Boston, Massachusetts</td>
<td>2003–2009</td>
<td>Patient/provider selected therapy; BMT provided through prescription and self-administered; MMT daily dosing at licensed clinic</td>
<td>Finnegan scale</td>
<td>Diluted tincture of opium; phenobarbital</td>
<td>Infants born before 35 weeks’ gestation; first-line NAS treatment changed over study period; small number of BMT-exposed neonates (n = 22)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Lacroix, 2011 (14)</td>
<td>Prospective multisite cohort</td>
<td>135 Mother-neonate pairs (125 livebirths)</td>
<td>France</td>
<td>1998–2006</td>
<td>Method of treatment choice and administration not provided; stricter follow-up for MMT than for BMT</td>
<td>Finnegan scale</td>
<td>Not provided</td>
<td>Rates of hepatitis B infection (for BMT group, 14.5%; for MMT group, 34.1%); use of heroin late in pregnancy (for BMT group, 12.9%; for MMT group, 35%)</td>
<td>Unadjusted and adjusted for heroin use in late pregnancy</td>
</tr>
<tr>
<td>Metz, 2011 (12)</td>
<td>Prospective cohort</td>
<td>77 Mother-neonate pairs at an addiction clinic</td>
<td>Vienna, Austria</td>
<td>2005–2009</td>
<td>Patient/provider selected therapy; observed BMT and MMT on clinic visit days, otherwise take-home doses</td>
<td>Modified Finnegan scale</td>
<td>Morphine hydrochloride</td>
<td>More severely addicted women received MMT</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Bakstad, 2009 (19)</td>
<td>Prospective cohort</td>
<td>38 Mother-neonate pairs in OMT programs</td>
<td>Norway</td>
<td>2005–2007</td>
<td>Therapy determined through OMT program; BMT and MMT provided by general practitioner following stabilization at OMT program regional center</td>
<td>Finnegan scale (most) or Lipsitz scale</td>
<td>Not provided</td>
<td>Years of illicit opioid use (for BMT group, 7 (SD, 3.7); for MMT group, 9 (SD, 2.9))</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Kakko 2008 (18)</td>
<td>Prospective (2001–2006 for BMT) and retrospective (1982–2006 for MMT) cohort</td>
<td>83 Mother-neonate pairs at an antenatal clinic</td>
<td>Stockholm, Sweden</td>
<td>2001–2006 (for BMT); 1982–2006 (for MMT)</td>
<td>Patient/provider selected appropriate therapy; daily supervised dosing at medical clinic until patient demonstrated treatment stability</td>
<td>Provider judgment (before 1996); Finnegan scale</td>
<td>Morphine (prospective); varied therapy (retropective)</td>
<td>Women receiving MMT were older; treatment began before conception (for BMT group, 57.5%; for MMT group, 82.9%); concomitant medication (for BMT group, 71%; for MMT group, 89%); positive toxicology screen during pregnancy (for BMT group, 32%; for MMT group, 49%)</td>
<td>Unadjusted and adjusted for maternal age</td>
</tr>
<tr>
<td>Colombini, 2008 (31)</td>
<td>Prospective cohort</td>
<td>22 Mother-infant pairs at Hospital Nord</td>
<td>Marseille, France</td>
<td>1998–2004</td>
<td>Not provided</td>
<td>Lipsitz scale</td>
<td>Morphine hydrochloride</td>
<td>Women receiving MMT were older</td>
<td>Unadjusted</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Design</th>
<th>Participants</th>
<th>Location</th>
<th>Years of Birth</th>
<th>NAS Treatment</th>
<th>NAS Assessment</th>
<th>NAS Treatment</th>
<th>Potential Sources of Bias</th>
<th>Analytical Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lejeune, 2006</td>
<td>Prospective</td>
<td>260 Mother-neonate pairs</td>
<td>France</td>
<td>1999-2003</td>
<td>BMT prescribed by public practitioner or MMT provided</td>
<td>Lipsitz scale</td>
<td>Morphine (72%); beginning (for BMT group, 17 years); other choice (3%); living with partner (for BMT group, 68%); for MMT group, 51%</td>
<td>Unadjusted</td>
<td>Unadjusted</td>
</tr>
</tbody>
</table>

Abbreviations: BMT, buprenorphine maintenance treatment; MMT, methadone maintenance treatment; NAS, neonatal abstinence syndrome; OMT, opioid maintenance treatment; RCT, randomized controlled trial; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

b There was no difference in length of NAS treatment or birth length.
c Adjustment made no difference in risk of NAS treatment.
d Excluded because it was an early publication of mother-neonate pairs in Norway who were later included in the article by Welle-Strand et al. (15).
e Excluded from the meta-analysis through our quality assessment because collection of data was primarily retrospective for MMT-exposed neonates and prospective for BMT-exposed neonates; different scoring criteria were used for indication for NAS treatment; varied first-line therapies were used in MMT-exposed neonates with NAS versus use of morphine in BMT-exposed neonates with NAS; and the time periods of study were different in the BMT and MMT groups.

RESULTS

Our search identified 298 published articles, most of which were not comparative studies of prenatal BMT exposure versus MMT exposure on neonates. The majority of identified articles were studies of other determinants or outcomes (e.g., MMT vs. heroin, smoking, breastfeeding, or social interventions; n = 103); descriptive studies of BMT or MMT or case reports (n = 66); review papers (n = 57); studies of NAS treatment, treatment guidelines, obstetrical care, or nursing care (n = 39); or other studies not meeting our criteria (n = 19). This latter group included 2 non–English-language letters describing a comparative study, which was later published in an English-language report and included in our meta-analysis (Table 1) (28). The remaining 14 published studies were comparative studies of prenatal BMT exposure versus MMT exposure; all were cohort studies or RCTs (Table 1). Three of the 4 RCTs had considerable dropout rates across treatment arms (11, 13, 29) and conducted per-protocol analysis as the primary analysis. One RCT had limited information on study methods (28). The largest RCT (11) also conducted a secondary analysis that adjusted for other factors, some of which may be potential confounders and some possibly causal intermediates. The method of prenatal agonist therapy administration differed across studies: in most of the RCTs, BMT and MMT were administered by observed daily dosing at the and augment better outcomes in the BMT group. In our simulations, the range of possible values of MD_{confounder, BMT} corresponded to a positive effect on the neonate, and MD_{confounder, MMT} corresponded to a harmful effect. Because empirical confounder data were unavailable, we estimated what we believed to be plausible values for the prevalence of confounding by indication (p_1 = p_0 = 0.40) and the effect of confounding using published study results (Web Table 1, available at http://aje.oxfordjournals.org/).

The analogous formula for the adjusted risk ratio (RR_{adjusted}) for our binary outcomes is

\[
RR_{adjusted} = \frac{RR_{unadjusted} \cdot (1 - p_0)}{RR_{confounder, MMT} \cdot p_0 + RR_{confounder, BMT} \cdot p_1}
\]

where RR_{unadjusted} is the unadjusted risk ratio estimated from our meta-analysis, RR_{confounder, MMT} is the relative effect of the confounder on the outcome in mother-neonate pairs assigned to MMT because of indication versus a reason other than indication, and RR_{confounder, BMT} is the relative effect of the confounder on the outcome in mother-neonate pairs assigned to BMT because of indication versus a reason other than indication.

Using a uniform distribution, we performed 10,000 simulations over the proposed range of the confounding effect for each study outcome. We reported the 25th-, 50th-, and 75th-percentile adjusted estimates for each of the 10,000 simulations. Statistical analyses were conducted using NCSS, version 8.0, software (NCSS, LLC, Kaysville, Utah), Meta-Analyst, version 9.0 (http://www.cebm.brown.edu/open_meta), and SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina).
study clinics (11, 13, 29); in the US cohort studies, only MMT was administered by observed daily dosing (10, 30); in cohort studies from France, women receiving MMT had stricter follow-up than those receiving BMT (14); in other European studies, take-home doses of BMT and MMT were permitted (12); and in some studies, treatment administration was not described (15–17, 28, 31). Most studies had fewer than 100 mother-neonate pairs and did not adjust for potential confounding. In our quality assessment of the published literature, we excluded 1 study from our meta-analysis because of study design limitations (18). In this study, collection of data was primarily retrospective for MMT-exposed subjects and prospective for BMT-exposed subjects, different scoring criteria were used for NAS treatment indication, various first-line therapies were used in MMT-exposed neonates with NAS versus morphine in BMT-exposed neonates with NAS, and the time periods of study were different in the BMT versus MMT groups. We also excluded an early publication (19) of mother-neonate pairs in Norway who were later included in a larger study (15). No other comparative studies were excluded.
A total of 515 BMT-exposed and 855 MMT-exposed neonates were included in the meta-analysis. Most summary estimates were based on fewer neonates because of data availability. The results of the meta-analysis of NAS outcomes are shown in Figure 1. The risk ratio of NAS treatment was 0.90 (95% confidence interval (CI): 0.81, 0.98) in BMT-exposed versus MMT-exposed neonates, and the average hospital stay was shorter (−7.23 days, 95% CI: −10.64, −3.83). Among infants treated for NAS, the length of treatment (−8.46 days, 95% CI: −14.48, −2.44) and the total amount of morphine used (−3.60 mg, 95% CI: −7.26, 0.07) were lower in BMT-exposed versus MMT-exposed neonates. Fewer women

Figure 1. Results of the meta-analysis of prenatal exposure to buprenorphine versus methadone and neonatal abstinence syndrome (NAS) outcomes of neonates born from 1996 to 2012. A) Risk ratio of treatment for NAS; B) mean difference in length of hospital stay (in days); C) mean difference in total morphine used to treat NAS (in mg); and D) mean difference in length of NAS treatment (in days). Bars, 95% confidence intervals.
who were treated prenatally with BMT versus MMT had il-
licit opioid use detected late in pregnancy (risk ratio = 0.44,
95% CI: 0.28, 0.70).

When we omitted 1 study at a time, pooled estimates for
NAS outcomes and maternal illicit opioid use late in preg-
nancy produced estimates close to our overall estimate and
with overlapping confidence intervals, suggesting that our
summary results were not driven by a particular study. When
summary estimates were run separately for each study design
(RCT and cohort), protective associations were found, but
confidence intervals were wider because of the smaller sam-
ple sizes. In simple meta-regression analyses, a cohort study
versus RCT design predicted a greater difference in the length
of NAS treatment and the amount of morphine treatment in
the BMT group versus the MMT group.

There was some heterogeneity across studies for NAS out-
comes but not for illicit maternal opioid use. The Cochran Q
test of homogeneity indicated significant variability across
studies for length of hospital stay, number of days of NAS
treatment, and amount of morphine needed to treat NAS. Galbraith plots showed that some studies had values that
were outside the ±2-unit boundary of the summary estimates
for NAS treatment (14), length of hospital stay (12), and
amount of morphine needed to treat NAS (11, 12). The $I^2$ sta-
tistic attributed 15% (NAS treatment), 85% (length of hospital stay), 60% (amount of morphine), and 81% (days of mor-
phine treatment) of the variation in estimates to heterogeneity
among studies. Funnel plots generally demonstrated a good
distribution of results by study size, although some were lim-
ited by a small number of studies (Figure 2). The funnel plot
for NAS treatment may suggest an absence of smaller pub-
lished studies showing a higher risk of NAS treatment in
BMT-exposed versus MMT-exposed neonates.

Figure 3 provides the results of the meta-analysis of birth
outcomes by prenatal exposure. Mean differences in gesta-
tional age at birth (0.89 weeks, 95% CI: 0.50, 1.29), birth

Figure 2. Funnel plots of prenatal exposure to buprenorphine versus methadone and neonatal abstinence syndrome (NAS) outcomes of neonates
born from 1996 to 2012. A) Risk ratio of treatment for NAS; B) mean difference in length of hospital stay (in days); C) mean difference in total mor-
phine used to treat NAS (in mg); and D) mean difference in length of NAS treatment (in days).
weight (243.63 g, 95% CI: 154.36, 332.91), body length (1.34 cm, 95% CI: 0.69, 1.99), and head circumference (0.87 cm, 95% CI: 0.45, 1.29) were higher in BMT-exposed versus MMT-exposed neonates. There was no difference in the risk of preterm birth (<37 vs. ≥37 weeks’ gestation) by exposure (risk ratio = 0.82, 95% CI: 0.46, 1.45). Pooled estimates omitting 1 study at a time suggested that our summary results were not driven by any particular study. In simple meta-regression analyses, study design was not associated with birth outcomes in the BMT-exposed versus the MMT-exposed group. The Cochran Q test of homogeneity and Galbraith plots did not suggest any heterogeneity across the study results for

The $I^2$ statistic was 0% for all birth outcomes except body length ($I^2 = 4\%$). Funnel plots suggested that differences in birth outcomes were unaffected by the size of the published study (Figure 4).

The results of our sensitivity analyses adjusting for possible unmeasured confounding by indication are shown in Table 2. Using our proposed prevalence and effect of the unmeasured confounder over 10,000 simulations, there was no
difference in the risk of NAS treatment, the total amount of morphine used to treat NAS, or the risk of preterm birth in BMT-exposed versus MMT-exposed neonates. Adjusted estimates for other NAS and birth outcomes were less marked than our unadjusted meta-analysis estimates but generally suggested better outcomes in BMT-exposed versus MMT-exposed neonates. Finally, in our simulations, confounding did not appear to explain the lower risk of illicit opioid use late in pregnancy in women treated with BMT versus MMT.

**DISCUSSION**

This meta-analysis pooled the findings of 12 original studies of prenatal BMT exposure versus MMT exposure on the neonate. Our unadjusted summary results show better NAS and birth outcomes in BMT-exposed versus MMT-exposed neonates and less illicit opioid use late in pregnancy in women treated with BMT versus MMT. However, these results must be considered in light of the potential for unmeasured confounding and other bias in the original studies. BMT and MMT are not only pharmacologically different, but in the United States, they represent different systems of care. Cohort studies have documented higher use of BMT in more stable opioid-dependent pregnant women who do not need the structure of observed daily MMT dosing (12, 14, 16, 17, 19). In the landmark Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial, rates of dropout were higher in mothers randomized to blinded BMT versus MMT, and mothers who continued to receive BMT versus MMT had less prior opioid use (11). In addition, women who receive opioid agonist therapy at conception may differ from women who become pregnant while actively using illicit opioids and then seek help for opioid use disorder. Of the studies included in our meta-analysis, 2 European studies recruited women from treatment programs, most of whom were receiving treatment at conception (14, 15), and in
Simulation Results Adjusted for Potential Unmeasured Confounding by Indication on the Association of Prenatal BMT Versus MMT on Pregnancy Outcomes

Table 2.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Range of Effect of Confounder on Outcome</th>
<th>Adjusted Association of BMT Versus MMT Over 10,000 Simulations, by Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assigned to BMT</td>
<td>Assigned to MMT</td>
</tr>
<tr>
<td></td>
<td>Because of Indication</td>
<td>Versus Other Reason</td>
</tr>
<tr>
<td></td>
<td>Risk Ratio</td>
<td>Mean Difference</td>
</tr>
<tr>
<td>NAS treatment</td>
<td>0.80–0.95</td>
<td>1.05–1.25</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>–10 to –1</td>
<td>1–10</td>
</tr>
<tr>
<td>Total morphine used to treat NAS (mg)</td>
<td>–5 to –1</td>
<td>1–5</td>
</tr>
<tr>
<td>Length of treatment (days)</td>
<td>–10 to –1</td>
<td>1–10</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>–7 to –1</td>
<td>1–7</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>0.80–0.95</td>
<td>1.05–1.25</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>100–300</td>
<td>–300 to –100</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>0.5–1.5</td>
<td>–1.5 to –0.5</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>0.25–1</td>
<td>–1 to –0.25</td>
</tr>
<tr>
<td>Maternal illicit opioid use late in pregnancy</td>
<td>0.5–0.95</td>
<td>1.1–2</td>
</tr>
</tbody>
</table>

Abbreviations: BMT, buprenorphine maintenance treatment; CI, confidence interval; MMT, methadone maintenance treatment; NAS, neonatal abstinence syndrome.
interesting that such heterogeneity was not observed in our birth outcomes. Recent articles have supported the inclusion of both cohort studies and RCTs in meta-analyses, because both types of study design have strengths and weaknesses; the inclusion of information from observational studies may improve causal inference, and meta-analyses based on observational studies generally produce estimates similar to those based on RCTs (37). A prior meta-analysis of 3 RCTs of prenataal BMT versus MMT reported that the trials were too few and too small to make any inference about the comparative effects of treatments (38). Further, when many patients do not adhere to randomized treatment and follow-up—as has been the case in RCTs of BMT versus MMT—the benefits of randomization are fewer and the trial becomes more like a nonexperimental cohort study. Our results from the meta-analysis of RCTs only were similar in direction to the summary estimates that included cohort studies. Finally, our study is limited by the lack of data on longer-term outcomes; few studies have followed these children beyond the first few years of life, and it is unknown whether in utero exposure to agonist therapies, NAS, or NAS treatment has long-term consequences on child development (18, 39).

Treating maternal opioid dependency with maintenance therapies may improve pregnancy outcomes; however, the risk of NAS is significant. The number of newborns with NAS in the United States is approximately 14,000 annually and continues to increase (40). Forty percent to 80% of exposed neonates develop withdrawal requiring prolonged hospitalization and pharmacotherapy with potential adverse effects. Evidence provided by this meta-analysis summarizes published research on prenatal exposure to BMT versus MMT on the neonate, all of which must be considered with respect to the potential for systematic error. Additional data are needed to better evaluate the impact of systematic error on study evidence and to inform clinicians and women in their treatment choices.

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