

Buprenorphine compared with methadone in pregnancy: a systematic review and meta-analysis

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Short Title: Opioid replacement in pregnancy

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Supplemental Table 1. Preferred Reporting Items for Systematic Review (PRISMA)

Section/topic	#	Checklist item	Page or Table/Figure Where Reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6 (+ supplement)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6 (+ supplement)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 (+ supplement)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Supplemental Table 2. Definitions of Population, Intervention, Comparator and Outcomes (PICO)

Population	Mothers who are pregnant and prescribed opioid substitutes and offspring that were exposed to opioids during their gestation
Intervention	Buprenorphine drug therapy (with or without naloxone)
Comparator	Methadone drug therapy
Outcomes	<p>Maternal outcomes: death, side-effects associated with treatment, maintenance on treatment, illicit drug use, and mode of delivery.</p> <p>Offspring outcomes: death, stillbirth, birthweight, small for gestational age, length (at birth), head circumference (at birth), prematurity, opioid withdrawal treatment, hospital stay, congenital anomalies and childhood development</p>

Supplemental Table 3. Definitions of outcomes of interest

Outcomes	Definition
Maternal death	Loss of life of mother
Side effects of medication	Maternal side effects associated with treatment
Maintenance on treatment	Maintenance on specific opioid replacement treatment
Mode of delivery	Type of delivery – SVD, assisted vaginal or caesarean section
Additional Opioid use	Use of illicit opioids through pregnancy
Stillbirths	Stillbirth offspring
Offspring death	Post-partum death of offspring
Birth weight	Total body weight at birth in grams
Length	Total body length at birth in centimetres
Head circumference	Head circumference at birth in centimetres
Small for gestational age	Rate of small for gestational age, definitions as per study
Prematurity	Birth before completion of 37 weeks gestation
NAS (Neonatal Abstinence Syndrome) Treatment	Requirement for treatment of neonatal withdrawal
Hospital stay	Duration of neonatal hospital admission in days
Congenital anomalies	Structural, metabolic, or functional defect present at birth or diagnosed as a neonate
Childhood development	Cognitive, functional, or behavioural development assessment

Supplemental Table 4. Search terms used per dataset

Medline	Embase	Cochrane Database of Systematic Reviews
<p>((((opiate substitution treatment [MeSH Major Topic]) OR buprenorphine) OR methadone) AND Humans [Mesh])) AND (((((infant[MeSH Major Topic]) OR neonat*[MeSH Major Topic]) OR neonat*) OR pregnan*[MeSH Major Topic]) OR pregnan*) Filters: Humans</p>	<p>Pregnancy OR newborn AND methadone OR buprenorphine OR “drugs used in treatment of addiction”</p>	<p>(MeSH (Pregnancy) OR MeSH(infant)) AND (MeSH Opiate Substitution Treatment) OR (Methadone) OR (Buprenorphine))</p>
Web of Science	Scopus	Open Gray
<p><i>(("opiate substitution treatment" OR buprenorphine OR methadone) AND (infan* OR neonat* OR pregnan*))</i></p>	<p>(Infan* OR neonat* OR pregnan*) AND (opiate substitution treatment OR buprenorphine OR methadone)</p>	<p>(buprenorphine OR methadone) AND pregnant</p>
Cinahl	Central	
<p>Pregnancy OR infant OR Neonate AND Opiate Substitution treatment OR methadone OR buprenorphine</p>	<p>Pregnancy OR Infant AND Opiate substitution treatment OR Methadone OR Buprenorphine</p>	

Supplemental Table 5. Risk of bias for cohort studies assessed by Newcastle Ottawa Scale (Wells, et al., 2014).

Study (year of publication)	Selection	Comparability	Outcome	Total stars
Beir (2015)	****	0 star	***	7
Brogly (2017)	***	**	***	8
Colombini (2008)	****	0 star	**	6
Ebner (2007)	****	0 star	**	6
Gawronski (2014)	****	0 star	***	7
Kakko (2008)	**	0 star	***	5
Konijnenberg (2014)	****	**	**	8
Lacroix (2011)	**	0 star	**	4
Lejeune (2006)	****	0 star	**	6
Meyer (2016)	****	**	***	9
Nechanska (2017)	****	**	***	9
Norgaard (2015)	****	**	**	8
Pritham (2013)	****	**	***	9
Tolia (2018)	**	**	***	7
Whitham (2010)	****	**	***	9
Wiegard (2015)	****	**	***	9

Supplemental Table 6. Assessment of bias in randomised studies via the Revised Cochrane Risk-of-Bias tool for randomised trials 2 (RoB 2) (Sterne, et al., 2019)

Study	Outcome	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Jones (2010)	Length at birth	+	+	-	+	+	-
Jones (2010)	Birth weight	+	+	-	+	+	-
Jones (2010)	Head circumference	+	+	-	+	+	-
Jones (2010)	Gestational age	+	+	-	+	+	-
Jones (2010)	Neonatal abstinence syndrome	+	+	-	+	+	-
Jones (2010)	Duration of hospital admission	+	+	-	!	+	-
Jones (2010)	Maternal outcomes	+	+	-	+	!	-
Jones (2010)	Prematurity	+	+	-	+	+	-
Jones (2010)	Caesarean section	+	+	-	+	+	-
Jones (2005)	Birth weight	+	+	-	+	!	-
Jones (2005)	Length at birth	+	+	-	+	!	-

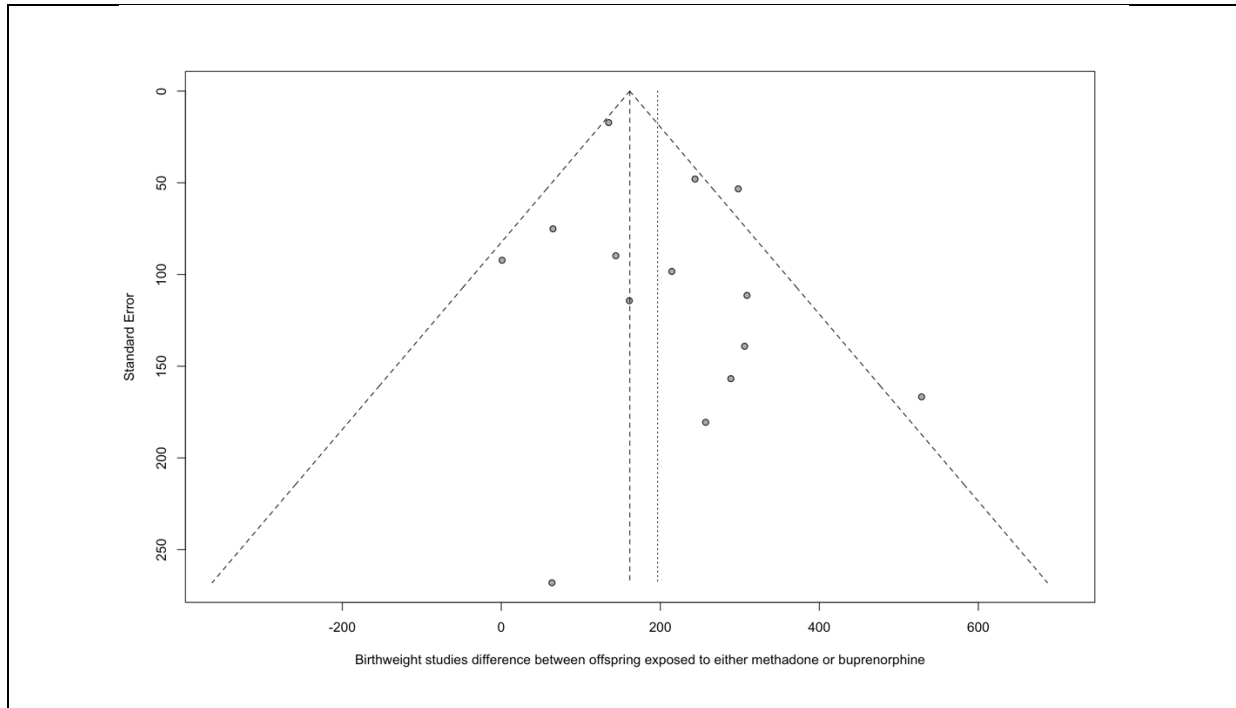
Jones (2005)	Head circumference	+	+	-	+	!	-
Jones (2005)	Gestational age	+	+	-	+	!	-
Jones (2005)	Neonatal abstinence syndrome	+	+	-	+	!	-
Jones (2010)	Stillbirth	+	+	-	+	!	-
Jones (2005)	Hospital stay	+	+	-	+	!	-
Jones (2005)	Prematurity	+	+	-	+	!	-
Jones (2005)	caesarean section	+	+	-	+	!	-
Jones (2005)	Stillbirth	+	+	-	+	!	-
Kaltenbach	Childhood outcomes	+	+	-	+	+	-
Fischer	Prematurity	+	+	-	+	!	-
Fischer	Gestational Age	+	+	-	+	!	-
Fischer	Stillbirth	+	+	-	+	!	-

Supplemental Table 7. Meta-analysis of cohort studies - adjusted and unadjusted pooled outcome measures

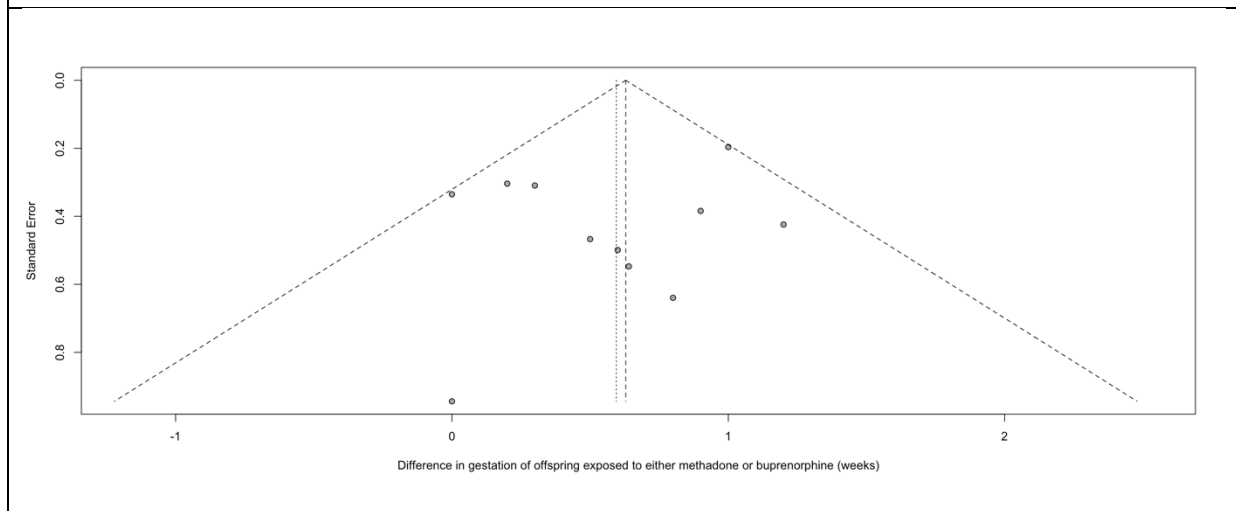
Outcome	Studies with adjusted estimates for outcomes	Pooled results (adjusted outcomes) ¹	Pooled results (unadjusted outcomes, all studies) ¹	Pooled results (adjusted where available plus unadjusted for remaining studies) ¹
Small for gestational age	Brogly (2017) Nechanska [CR] (2017) Nechanska [Nor] (2017)	RR 1.10 (95% CI: 0.79 - 1.52)	RR 0.76 (95% CI: 0.66 to 0.88)	RR 0.88 (95% CI: 0.67 to 1.15)
Prematurity	Brogly (2017) Nechanska [CR] (2017) Nechanska [Nor] (2017)	RR 0.66 (95% CI: 0.42 - 1.04)	RR 0.62 (95% CI: 0.53 to 0.74)	RR 0.60 (95% CI: 0.50 - 0.73)
Duration of hospital admission	Brogly (2017)	Mean Difference -3.66 (95% CI: -5.46 - -1.87)	WMD -6.84 days (95% CI: -11.37days - -2.32days)	NA ²
NAS (Neonatal Abstinence Syndrome) Treatment	Lacroix (2010) ³ Nechanska [Nor] (2017) Wiegard (2015)	RR 1.18 (95% CI: 0.78 - 1.79)	RR 0.58 (95% CI: 0.40 - 0.82)	RR 0.60 (95% CI: 0.50 - 0.73)

1. Results of buprenorphine compared to methadone, with methadone as reference group
2. Adjusted and non-adjusted estimates not pooled as data could not be combined to form total estimate of effect
3. Adjustment of NAS requirements given maternal heroin use.

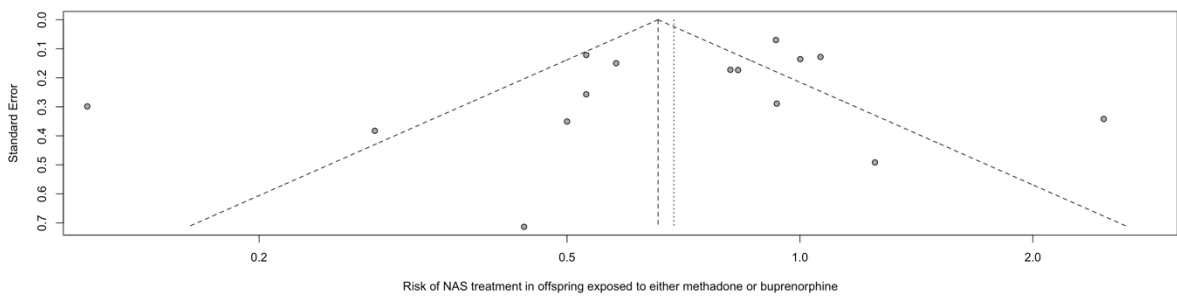
Supplemental Figure 1. Funnel plots for outcomes measured in which ten or more studies have reported results



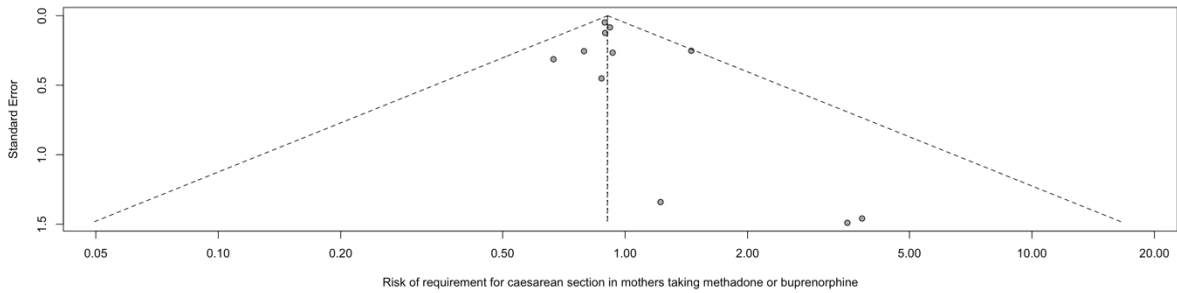
Supplemental Fig. 1.a Funnel plot of standard error for studies reporting birthweight of offspring following exposed buprenorphine or methadone.



Supplemental Fig. 1.b Funnel plot of standard error for studies reporting gestation of offspring following exposed buprenorphine or methadone

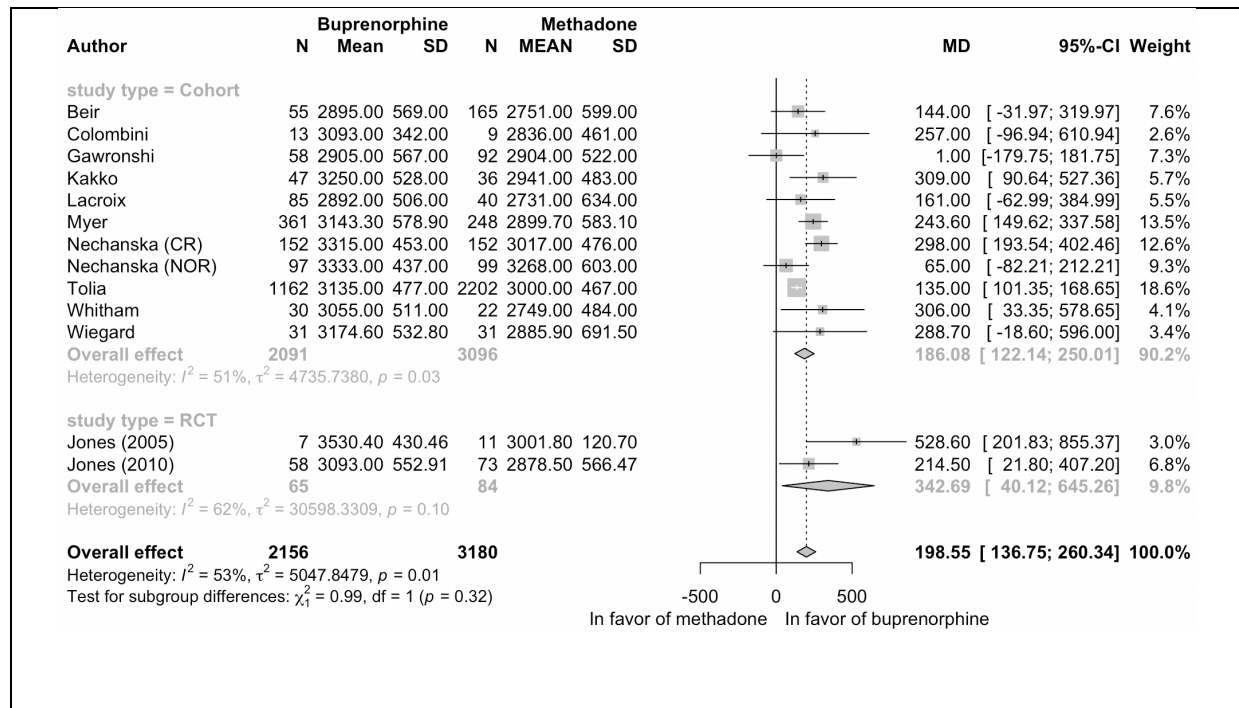


Supplemental Fig. 1.c Funnel plot of standard errors of studies reporting percentage per group treated for NAS

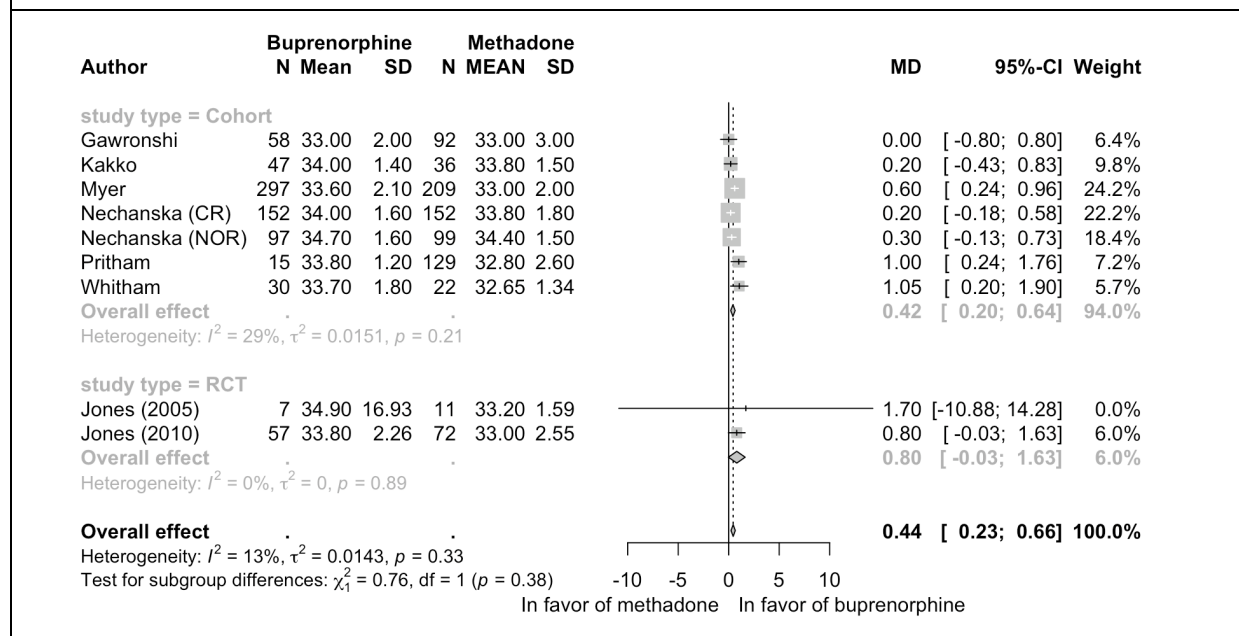


Supplemental Fig. 1.d Funnel plot of standard errors for caesarean section rate in mothers taking methadone or buprenorphine.

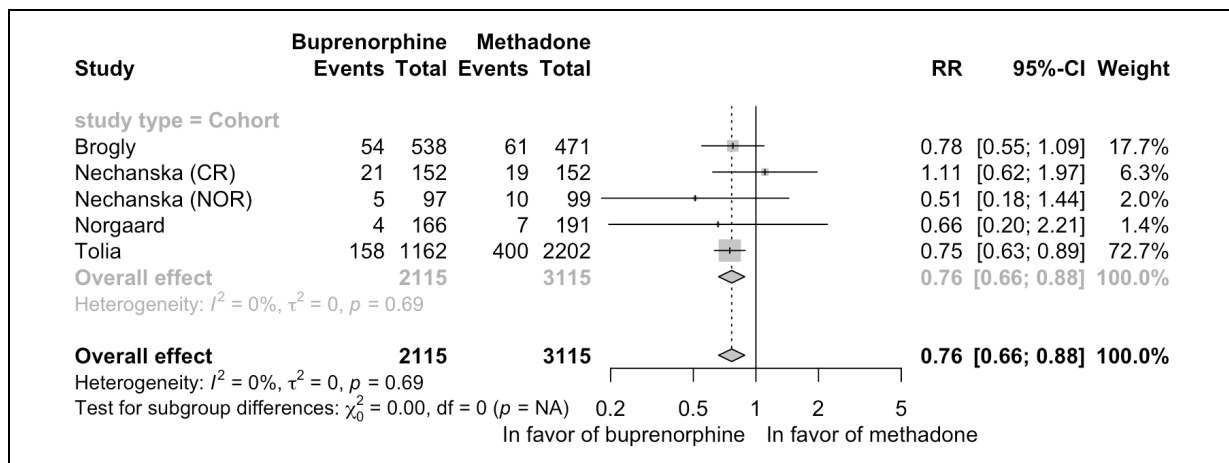
Supplemental Figure 2. Meta-analysis for each outcome



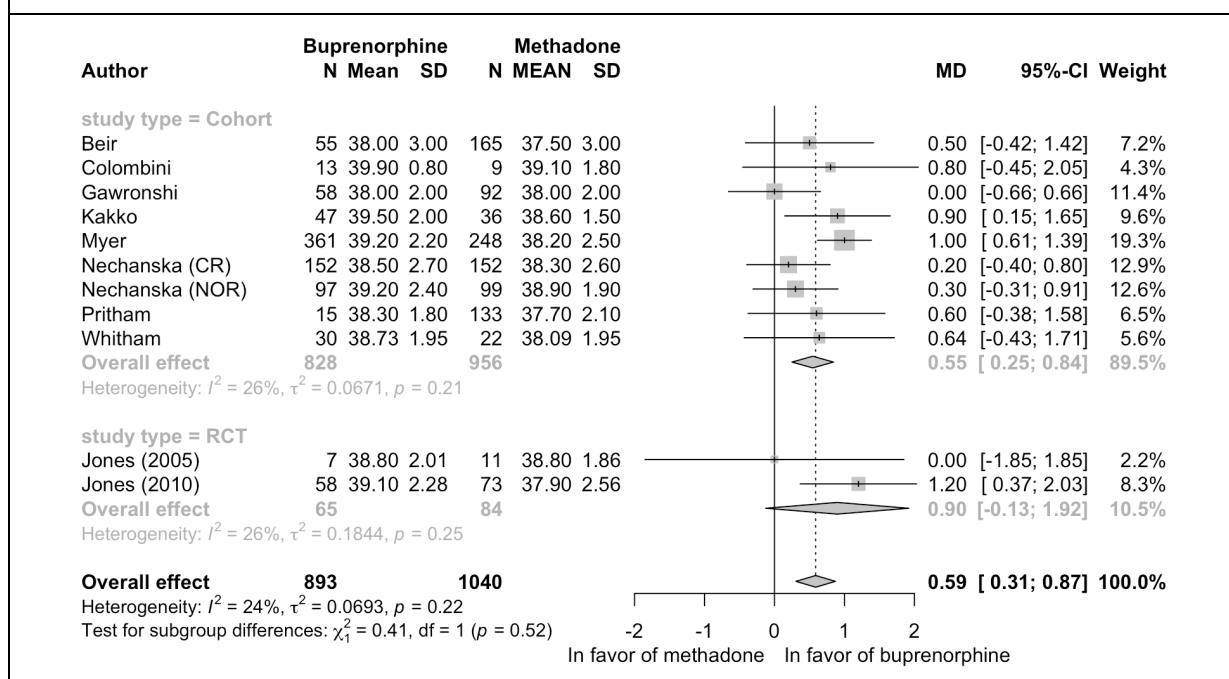
Supplemental Fig. 2.a – Meta-analysis of weighted mean difference of offspring’s birth weight in those exposure to buprenorphine or methadone during gestation with outlier removed, in grams.



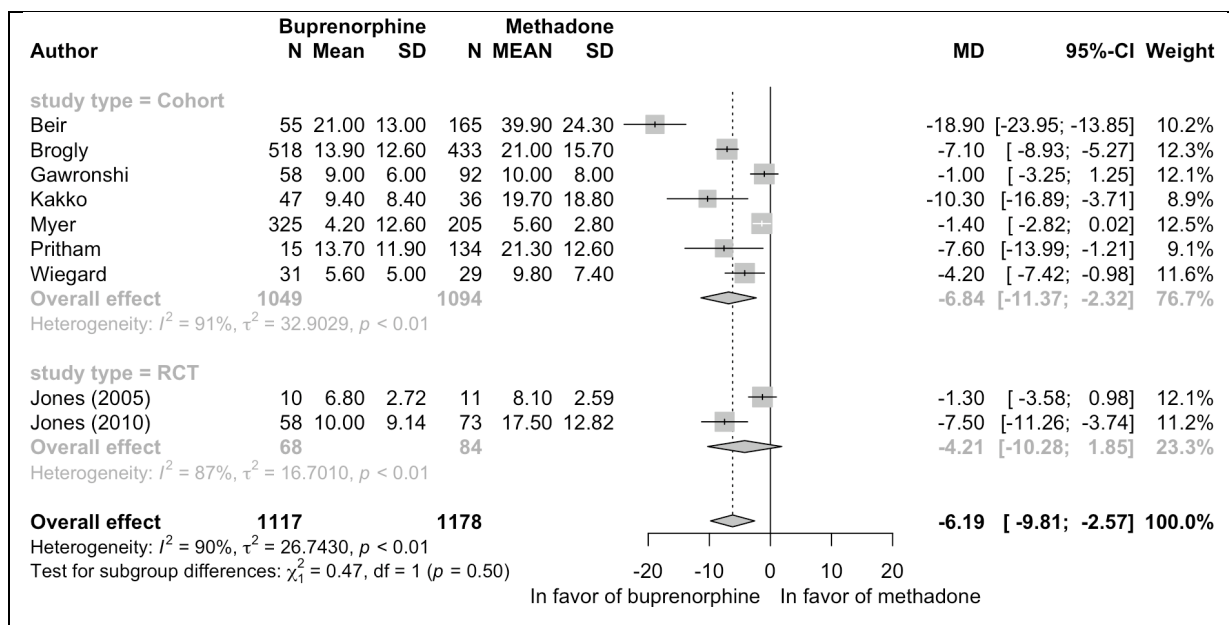
Supplemental Fig. 2.b – Meta-analysis of the weighted mean difference of offspring’s head circumference after exposure to buprenorphine or methadone during gestation, in centimetres.



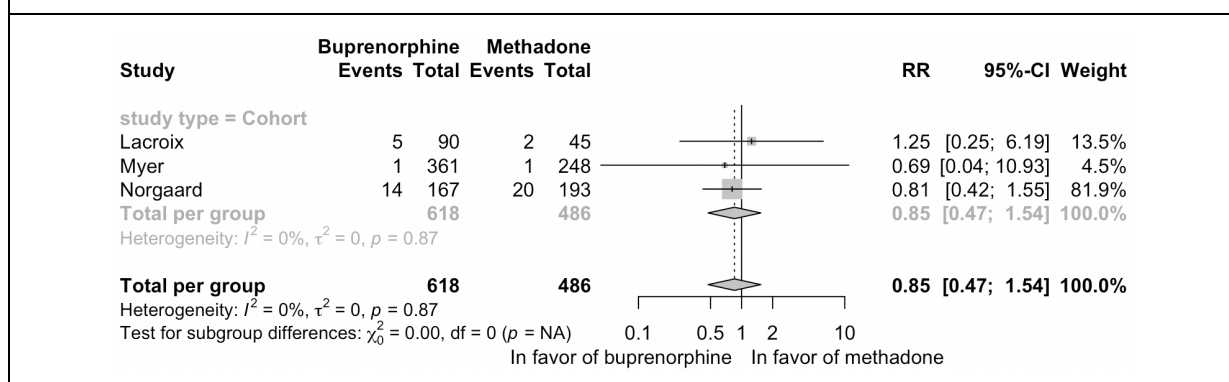
Supplemental Fig. 2.c – Meta-analysis of the relative risk of small for gestation age after exposure to buprenorphine or methadone during gestation.



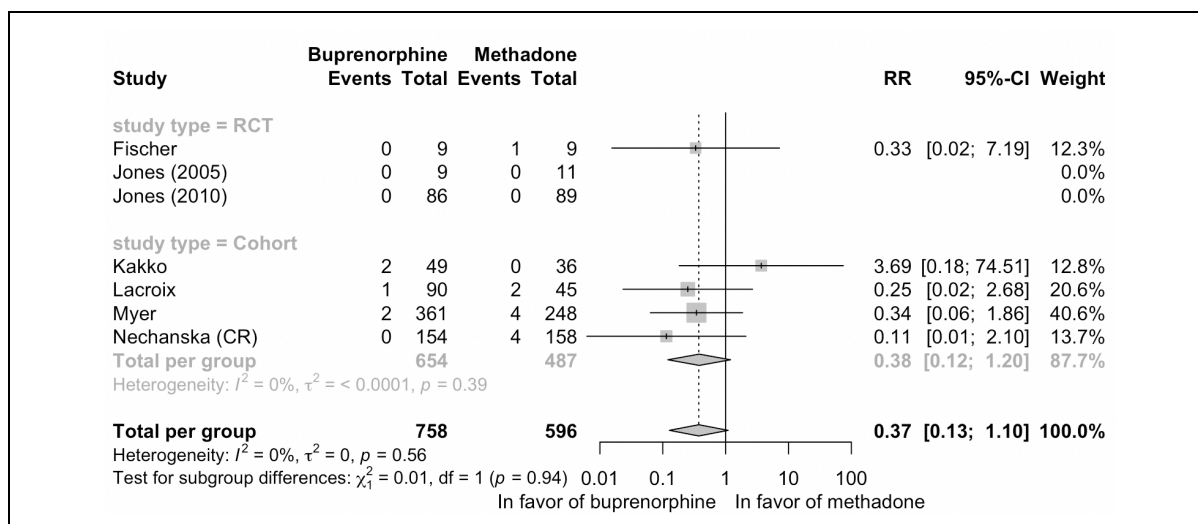
Supplemental Fig. 2.d Meta-analysis of the weighted mean difference in gestational age of offspring exposure to buprenorphine or methadone.



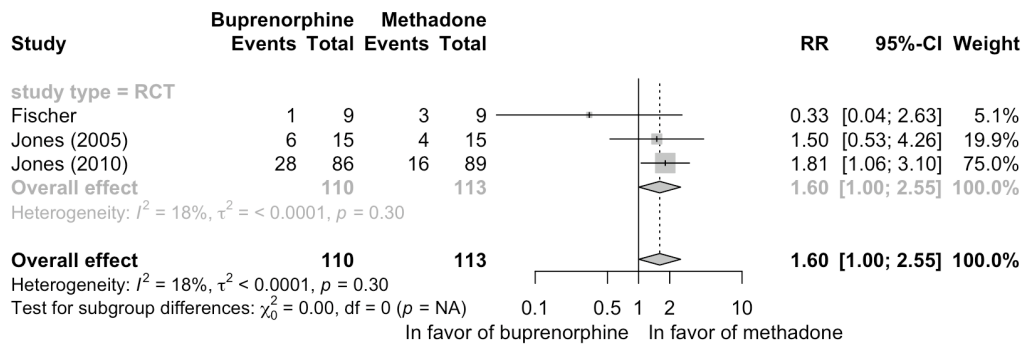
Supplemental Fig. 2.e Meta-analysis of the weighted mean difference in duration of hospital admission for offspring exposure to buprenorphine or methadone.



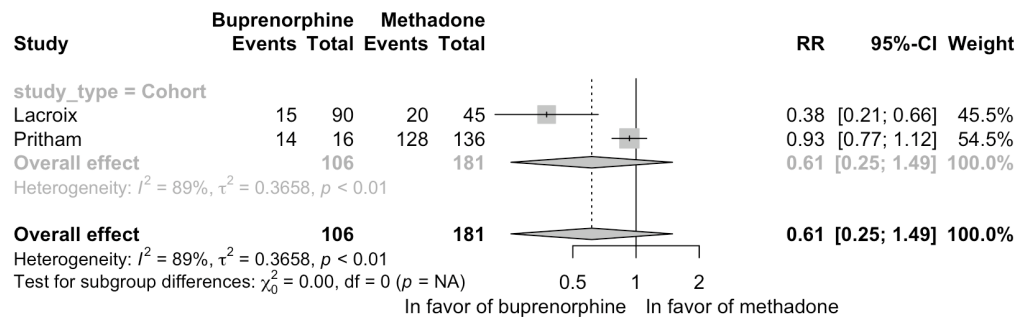
Supplemental Fig. 2.f - Meta-analysis of relative risk of congenital malformation required after exposure to buprenorphine or methadone during gestation.



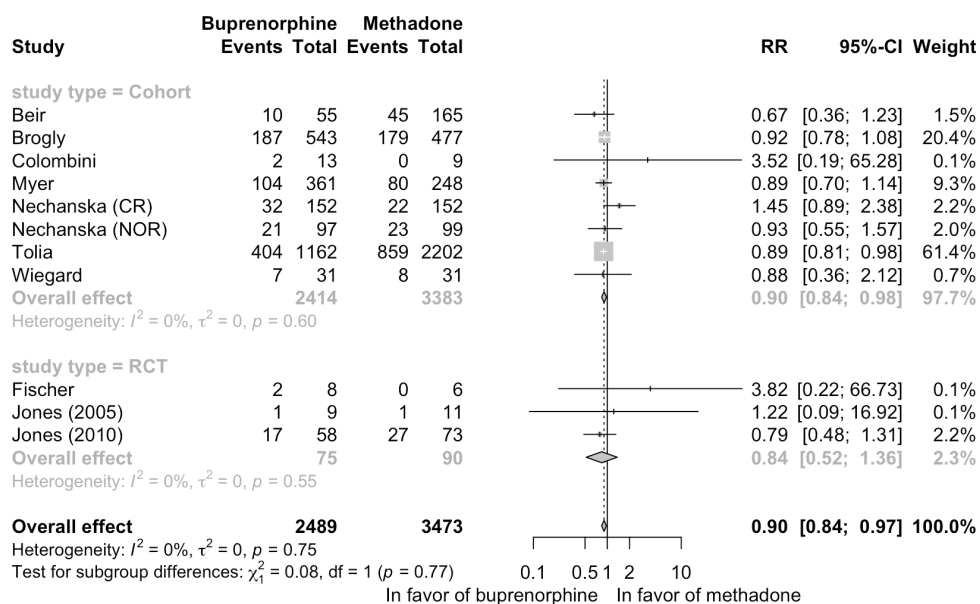
Supplemental Fig. 2.g - Meta-analysis of relative risk of stillbirth after exposure to buprenorphine or methadone during gestation.



Supplemental Fig. 2.h - Meta-analysis of relative risk of drop out use after exposure to buprenorphine or methadone.



Supplemental Fig. 2.i - Meta-analysis of relative risk of opioid use after exposure to buprenorphine or methadone.



Supplemental Fig. 2.j – Meta-analysis of relative risk of caesarean section after exposure to buprenorphine or methadone during gestation

