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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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
INTRODUC	TION	1	
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		<u> </u>	
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

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

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	Maternal outcomes: death, side-effects associated with treatment, maintenance on treatment, illicit drug use, and mode of delivery. 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

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
(((((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	Pregnancy OR newborn AND methadone OR buprenorphine OR "drugs used in treatment of addiction"	(MeSH (Pregnancy) OR MeSH(infant)) AND (MeSH Opiate Substition Treatment) OR (Methadone) OR (Buprenorphine))
Web of Science	Scopus	Open Gray
(("opiate substitution treatment" OR buprenorp hine OR methadone) AN D (infan* OR neonat* OR pregnan*)	(Infan* OR neonat* OR pregnan*) AND (opiate substation treatment OR buprenorphine OR methadone)	(buprenorphine OR methadone) AND pregnant
Cinahl	Central	
Pregnancy OR infant OR Neonate AND Opiate Substitution treatment OR methadone OR buprenorphine	Pregnancy OR Infant AND Opiate substitution treatment OR Methadone OR Buprenorphine	

Supplemental	Table 5. Risk of bi	as for cohort studie	es assessed by	Newcastle Ottaw	va Scale ((Wells, et
al., 2014).						

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

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)

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

Jones (2005)	Head circumference	+	+	-	+	!	-
<mark>Jones (2005)</mark>	Gestational age	\bullet	\bullet	-	•	!	-
<mark>Jones (2005)</mark>	Neonatal abstinence syndrome	•	+	-	•	!	-
<mark>Jones (2010)</mark>	<mark>Stillbirth</mark>	+	+		+	!	-
<mark>Jones (2005)</mark>	Hospital stay	+	+		+	!	-
Jones (2005)	Prematurity	\bullet	+		+	!	-
Jones (2005)	caesarean section	+	+		+	!	-
Jones (2005)	<mark>Stillbirth</mark>	+	+		+	!	-
Kaltenbach	Childhood outcomes		+	•	•	•	-
Fischer	Prematurity		+	-	•	!	-
Fischer	Gestational Age	+	+	-	+	!	-
<mark>Fischer</mark>	<mark>Stillbirth</mark>	-	+		•	!	-

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

 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 Figure 2. Meta-analysis for each outcome



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.

Author	Buprenorph N Mean	hine SD	N	Metha MEAN	done SD		MD	95%-CI	Weight
study type = Cohort									
Beir	55 38.00 3	3.00	165	37.50	3.00		0.50	[-0.42; 1.42]	7.2%
Colombini	13 39.90 (0.80	9	39.10	1.80		0.80	[-0.45; 2.05]	4.3%
Gawronshi	58 38.00 2	2.00	92	38.00	2.00		0.00	[-0.66; 0.66]	11.4%
Kakko	47 39.50 2	2.00	36	38.60	1.50		0.90	[0.15; 1.65]	9.6%
Myer	361 39.20 2	2.20	248	38.20	2.50		1.00	[0.61; 1.39]	19.3%
Nechanska (CR)	152 38.50 2	2.70	152	38.30	2.60		0.20	[-0.40; 0.80]	12.9%
Nechanska (NOR)	97 39.20 2	2.40	99	38.90	1.90		0.30	[-0.31; 0.91]	12.6%
Pritham	15 38.30	1.80	133	37.70	2.10		0.60	[-0.38; 1.58]	6.5%
Whitham	30 38.73	1.95	22	38.09	1.95		0.64	[-0.43; 1.71]	5.6%
Overall effect	828		956				0.55	[0.25; 0.84]	89.5%
Heterogeneity: $I^2 = 26\%$,	$\tau^2 = 0.0671, p$	= 0.21							
study type = RCT									
Jones (2005)	7 38.80 2	2.01	11	38.80	1.86		0.00	[-1.85; 1.85]	2.2%
Jones (2010)	58 39.10 2	2.28	73	37.90	2.56		1.20	[0.37; 2.03]	8.3%
Overall effect	65		84				0.90	[-0.13; 1.92]	10.5%
Heterogeneity: $I^2 = 26\%$,	$\tau^2 = 0.1844, p$	= 0.25							
Overall effect	893	1	040				0.59	[0.31; 0.87]	100.0%
Heterogeneity: I ² = 24%,	$\tau^2 = 0.0693, p$	= 0.22							
Test for subgroup differe	nces: χ ₁ ² = 0.41,	, df = 1	(p =	0.52)		2 -1 0 1 2			
				li li	n favo	of methadone In favor of bupr	enorp	hine	

exposure to buprenorphine or methadone.

Author	Buprenorp N Mean	ohine SD N	Methadone MEAN SD		MD	95%-CI Weight
study type = Cohort				: 1		
Beir	55 21.00 ²	13.00 165	39.90 24.30		-18.90 [-2	3.95: -13.851 10.2%
Brogly	518 13.90	12.60 433	21.00 15.70		-7.10	-8.93: -5.271 12.3%
Gawronshi	58 9.00	6 00 92	10.00 8.00		-1 00 [-3 25 1 25 12 1%
Kakko	47 940	8 40 36	19 70 18 80		-10.30	16 89: -3 711 8 9%
Mver	325 4 20	12 60 205	5.60 2.80	_	-140 [-2.82: 0.021 12.5%
Pritham	15 13 70	11 90 134	21.30 12.60		-7.60 [-	13.99 -1.211 9.1%
Wiegard	31 5.60	5.00 29	980 740		-4 20 [-7 42: -0.981 11.6%
Overall effect	1049	1094	0.00 7.10	$\langle \rangle$	-6.84 [-1	1.37: -2.32] 76.7%
Heterogeneity: $I^2 = 91\%$,	$\tau^2 = 32.9029, p$	< 0.01			0.01	
study type = PCT						
longe (2005)	10 6 90	2 72 11	9 10 2 50		1 20 [3 59. 0 091 12 1%
Jones (2005)	10 0.00 59 10 00	2.72 11	0.10 2.09		-1.30 [7.50 [-3.30, 0.90] 12.1%
Jones (2010)	58 10.00	9.14 73	17.50 12.62		-7.50 [-	11.20, -3.74] 11.2%
Hotorogonoity: $l^2 = 87\%$	$-^2 - 167010$ p	- 0.01			-4.ZI [-	10.20, 1.05] 25.570
Heterogeneity: $T = 67\%$,	$\tau = 10.7010, p$	< 0.01				
Overall effect	1117	1179			6 10 T	0 81: 2 571 100 0%
Hotorogonoity: $I^2 = 0.0\%$	$r^2 = 26.7430$ p.	~ 0.01				-9.61, -2.57] 100.0%
Helefogeneity. $I = 30 \%$,	$\tau = 20.7430, p$	< 0.01				
Test for subgroup differen	$n \cos x^2 = 0.47$	df = 1 (n = 0)	50)	-20 -10 0 10	20	
Test for subgroup differen	nces: $\chi_1^2 = 0.47$, c	df = 1 (p = 0.	.50) In favor of	-20 -10 0 10	20 methadone	
Test for subgroup differen	nces: $\chi_1^2 = 0.47$, c	df = 1 (p = 0.	50) In favor of	-20 -10 0 10 buprenorphine In favor of	20 methadone	
Test for subgroup differen	nces: $\chi_1^2 = 0.47$, c	df = 1 (p = 0)	50) In favor of	-20 -10 0 10 buprenorphine In favor of	20 methadone	hospital
Test for subgroup differen	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar	$df = 1 \ (p = 0)$	50) In favor of	-20 -10 0 10 buprenorphine In favor of ed mean difference in	20 methadone duration of	hospital
Test for subgroup different Supplemental Fig.	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi	df = 1 (p = 0) $nalysis of$ $ure to bu$	50) In favor of the weighte prenorphine	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone <mark>duration of</mark>	hospital
Test for subgroup differen Supplemental Fig. admission for offs	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi	df = 1 (p = 0)	50) In favor of the weighte prenorphine	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone duration of	hospital
Test for subgroup differen Supplemental Fig. admission for offs	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer	$\frac{df = 1}{p = 0}$	50) In favor of f the weighte prenorphine Methadone	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone duration of	
Test for subgroup differen Supplemental Fig. admission for offs Study	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer Ever	$\frac{df = 1 \ (p = 0)}{ure \ to \ bu}$ norphine nts Total E	50) In favor of f the weighte prenorphine Methadone ivents Total	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone duration of RR 95%	<mark>hospital</mark> 6-Cl Weight
Test for subgroup different Supplemental Fig. admission for offs Study study type =	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer Ever Cohort	df = 1 (p = 0. nalysis of ure to bu norphine nts Total E	50) In favor of <u>f the weighto</u> prenorphine Methadone ivents Total	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone duration of RR 95%	hospital 6-Cl Weight
Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer Ever Cohort	$\frac{df = 1 \ (p = 0)}{\frac{nalysis}{ure} to bu}$	50) In favor of f the weighte prenorphine Methadone ivents Total 2 45	-20 -10 0 10 buprenorphine In favor of cd mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6	hospital 6-Cl Weight .19] 13.5%
Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix Myer	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer Ever Cohort	$\frac{df = 1 \ (p = 0)}{\frac{nalysis}{ure} to bu}$	50) In favor of f the weighte prenorphine Methadone Events Total 2 45 1 248 —	-20 -10 0 10 buprenorphine In favor of cd mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10	hospital 6-Cl Weight .19] 13.5% .93] 4.5%
Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix Myer Norgaard	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer Ever Cohort	$\frac{df = 1 \ (p = 0)}{\text{nalysis of}}$ $\frac{1}{\text{ure to bu}}$ $\frac{1}{\text{norphine}}$ $\frac{5}{1} \frac{90}{361}$ $\frac{1}{14} \frac{361}{167}$	50) In favor of the weighte prenorphine Methadone vents Total 2 45 1 248 – 20 193	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10 0.81 [0.42; 1	hospital 6-Cl Weight .19] 13.5% .93] 4.5% .55] 81.9%
Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix Myer Norgaard Total per gro	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposu Buprer Ever Cohort	$\frac{df = 1 \ (p = 0)}{\text{nalysis of}}$ $\frac{df = 1 \ (p = 0)}{\text{ure to bu}}$ $\frac{df = 1 \ (p = 0)}{\text{norphine}}$ $\frac{f = 0}{\text{norphine}}$	50) In favor of the weighte prenorphine Methadone ivents Total 2 45 1 248 – 20 193 486	-20 -10 0 10 buprenorphine In favor of ed mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10 0.81 [0.42; 1 0.85 [0.47; 1	hospital 6-CI Weight .19] 13.5% .93] 4.5% .55] 81.9% .54] 100.0%
Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix Myer Norgaard Total per gro Heterogeneity:	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Bupren Ever Cohort pup $l^2 = 0\%$, $\tau^2 = 0$, p	df = 1 (p = 0) $nalysis of$ $ure to bu$ $norphine$ $nts Total E$ $5 90$ $1 361$ $14 167$ 618 $p = 0.87$	50) In favor of f the weighte prenorphine Methadone Events Total 2 45 1 248 – 20 193 486	-20 -10 0 10 buprenorphine In favor of cd mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10 0.81 [0.42; 1 0.85 [0.47; 1	hospital 6-Cl Weight .19] 13.5% .93] 4.5% .55] 81.9% .54] 100.0%
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Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix Myer Norgaard Total per gro Heterogeneity: Total per gro	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Bupren Ever Cohort pup $l^2 = 0\%$, $\tau^2 = 0$, p	df = 1 (p = 0) $nalysis of$ $ure to bu$ $norphine$ $norphine$ $5 90$ $1 361$ $14 167$ 618 $p = 0.87$ 618	50) In favor of f the weighte prenorphine Methadone Events Total 2 45 1 248 – 20 193 486 486	-20 -10 0 10 buprenorphine In favor of cd mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10 0.81 [0.42; 1 0.85 [0.47; 1	hospital 6-Cl Weight .19] 13.5% .93] 4.5% .55] 81.9% .54] 100.0%
Supplemental Fig. admission for offs Study study type = Lacroix Myer Norgaard Total per gro Heterogeneity: Total per gro Heterogeneity:	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Buprer Ever Cohort pup $l^2 = 0\%$, $\tau^2 = 0$, p pup differences τ^2	df = 1 (p = 0.) $nalysis of ure to bu$ norphine $fs Total E$ $5 90$ $1 361$ $14 167$ 618 $p = 0.87$ 618 $p = 0.87$	50) In favor of the weighte prenorphine Methadone vents Total 2 45 1 248 — 20 193 486 486 0 (n = NA)	-20 -10 0 10 buprenorphine In favor of cd mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10 0.81 [0.42; 1 0.85 [0.47; 1	hospital 6-Cl Weight .19] 13.5% .93] 4.5% .55] 81.9% .54] 100.0%
Test for subgroup different Supplemental Fig. admission for offs Study study type = Lacroix Myer Norgaard Total per gro Heterogeneity: Test for subgro	nces: $\chi_1^2 = 0.47$, c 2.e Meta-ar pring exposi Bupren Ever Cohort pup $l^2 = 0\%, \tau^2 = 0, p$ pup differences: χ_1^2	df = 1 (p = 0.) $nalysis of$ $ure to bu$ $norphine$ $nts Total E$ $5 90$ $1 361$ $14 167$ 618 $p = 0.87$ 618 $p = 0.87$ $c = 0.00, df = 0.00$	50) In favor of the weighte prenorphine Methadone vents Total 2 45 1 248 — 20 193 486 486 0 (p = NA) In favor of h	-20 -10 0 10 buprenorphine In favor of cd mean difference in or methadone.	20 methadone duration of RR 95% 1.25 [0.25; 6 0.69 [0.04; 10 0.81 [0.42; 1 0.85 [0.47; 1 0.85 [0.47; 1	hospital 6-CI Weight .19] 13.5% .93] 4.5% .55] 81.9% .54] 100.0%
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exposure to buprenorphine or methadone during gestation.

Study	Events	Total	Events	Total		RR	95%-CI	Weight
study type = RCT								
Fischer	0	9	1	9		0.33	[0.02; 7.19]	12.3%
Jones (2005)	0	9	0	11				0.0%
Jones (2010)	0	86	0	89				0.0%
study type = Cohor	t							
Kakko	2	49	0	36		- 3.69	[0.18; 74.51]	12.8%
Lacroix	1	90	2	45		0.25	[0.02; 2.68]	20.6%
Myer	2	361	4	248	_	0.34	[0.06; 1.86]	40.6%
Nechanska (CR)	0	154	4	158		0.11	[0.01; 2.10]	13.7%
Total per group		654		487	\sim	0.38	[0.12; 1.20]	87.7%
Heterogeneity: $I^2 = 0\%$	$t_{\rm o}, \tau^2 = < 0.000$	01, p =	0.39					
Total per group		758		596		0.37	[0.13; 1.10]	100.0%
Heterogeneity: $I^2 = 0\%$	$f_{\rm p}, \tau^2 = 0, p = 0$	0.56						
Test for subgroup diffe	rences: $\gamma_1^2 = 0$	0.01 dt	f = 1 (p = 1)	0.94) (01 01 1 10	100		

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



buprenorphine or methadone during gestation