

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

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)

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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 2015 USA	1996 – 2014	Retrospective cohort study	220 165 methadone 55 buprenorphine	Developmental Paediatric clinic, USA	Inclusion: All offspring born in clinic during study period Exclusion: Not specified	<p>Total birth weight of offspring: methadone 2751g (SD \pm 599), buprenorphine 2895g (SD \pm 569)</p> <p>Gestational age at birth: methadone 37.5weeks (SD \pm 3), buprenorphine 38weeks (SD \pm 3)</p> <p>Prematurity: methadone 31 (19%), buprenorphine 5 (9%)</p> <p>Treatment for NAS: methadone 145 (88%), buprenorphine 45 (82%)</p> <p>Length of offspring hospital admission: methadone 39.9 (SD \pm 24.3) buprenorphine 21 (SD \pm13)</p> <p>Caesarean section rate: methadone 45 (27%), buprenorphine (18%)</p> <p>Development assessment: Bayley Mental Development Index Low dose methadone: 96.6(SD \pm7), high dose methadone 94.3(SD \pm 9) buprenorphine 95.7(SD \pm 7).</p> <p>Alberta Infant motor score: Low dose methadone: 44.8(SD \pm24), High dose methadone 38.1(SD \pm24), buprenorphine 53.5 (SD\pm2).</p> <p>Suspect or abnormal neurological exam Low dose methadone: 19 (23%), high dose methadone 17 (21%), buprenorphine 7 (13%)</p> <p>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.</p>	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) Caesarean Section: methadone 179 (37.5%), buprenorphine 187 (34.3%)	Adjustments for maternal age, race/ethnicity, year of delivery, pre-natal selective serotone 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)
Colom bini 2007 France	1998 – 2004	Prospective cohort study	21 9 methadone 13 buprenorphine	Single addiction centre 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%) Caesarean section: methadone 90 (0%), buprenorphine 2 (15%) Onset of NAS (range – hrs): methadone 6-24hrs, buprenorphine 24-168hrs. Not analysed in meta- analysis as only range presented.	No adjusted results published.

Ebner 2007 Austria	Not specifi ed	Prospective cohort study	36 22 methadone 14 buprenorphine	Single Specialist clinic in Austria	<p>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.</p> <p>Exclusion: Neonates born to mothers with alcohol and/or benzodiazepine co-dependency and twin pregnancies</p>	<p>Treatment for NAS: methadone 7(32%), buprenorphine 11 (74%)</p> <p>Time to develop NAS: methadone 57.5hrs (SD ± 37.5), buprenorphine 34.4hrs (SD ± 5.3)</p> <p>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.</p>	No adjusted results published.
Fischer 2005 Austria	2000 - 2002	Randomised control trial	18 9 methadone 9 buprenorphine	Single addiction clinic at the Medical University of Vienna, Austria	<p>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.</p> <p>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.</p>	<p>Pre-term delivery (<37 weeks): methadone 3, buprenorphine 2,</p> <p>Treatment for NAS: 8 required treatments 3 in methadone group (50%), 5 in buprenorphine group (63%)</p> <p>Start of Treatment for NAS methadone 60hrs (SD11.3), buprenorphine 72hrs (SD 35.2)</p> <p>Caesarean section: methadone group 0, buprenorphine group 0</p> <p>Dropouts of treatment: methadone 3, buprenorphine 1</p> <p>Total birth weight of offspring mean: 2820g – not reported per group except for “no difference” therefore not analysed.</p>	No adjusted results published.

Gawronski 2014 USA	2010 – 2011	Retrospective cohort study	150 92 methadone 58 buprenorphine	Single centre medical centre Ohio (USA).	<p>Inclusion: 18 years of age with a history of opioid dependence currently enrolled in a treatment program and stabilized on buprenorphine/naloxone or methadone</p> <p>Exclusion: not specified</p>	<p>Total birth weight of offspring: methadone 2905g (SD ± 567), buprenorphine 2904(SD ± 522)</p> <p>Total body length of offspring at birth: methadone 49cm (SD ± 4), buprenorphine 49 cm (SD ± 4)</p> <p>Head Circumference: methadone 33cm (SD ± 3), buprenorphine 33cm (SD±3)</p> <p>Preterm birth: methadone 22 (24%), buprenorphine 10 (17%).</p> <p>Gestational age at birth: methadone 37weeks (SD ± 2), buprenorphine 38weeks (SD ± 2)</p> <p>Treatment for NAS: methadone 74 (80%), buprenorphine 37 (64%)</p> <p>Time to NAS onset: methadone 2days (range 1-9), buprenorphine 2 days (range 1-6). No analysed in meta-analysis due to unit of measure not being hours and only ranges presented.</p> <p>Length of offspring hospital admission: 10 days (SD ± 8), buprenorphine 9days (SD ± 6)</p> <p>Caesarean section: 20% - not analysed in meta-analysis as no group break down.</p>	No adjusted results published.
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Jones 2005 USA	2000 – 2003	Randomised control trial	30 15 methadone 15 buprenorphine	Single centre - Centre for Addiction and Pregnancy, USA.	<p>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.</p> <p>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 labour; evidence of foetal malformation; positive HIV test; or positive sickle cell trait</p>	<p>Total birth weight of offspring: methadone 3001.8g(SE ± 120.7), buprenorphine 3530.4g(SE ± 162.7)</p> <p>Head circumference: methadone 33.2cm (SE ± 0.48), buprenorphine 34.9cm (SE ± 6.40)</p> <p>Gestation: methadone 38.8weeks (SE ± 0.56), buprenorphine 38.8 weeks (SE ± 0.76)</p> <p>Preterm births: methadone 1 (9.1%), buprenorphine 0(0.0%)</p> <p>Treatment for NAS: methadone 5(45%), buprenorphine 2 (20%)</p> <p>Duration of hospital stay: methadone 8.1days (SE ±0.78), buprenorphine 6.8 days (SE ± 0.86)</p> <p>Caesarean section: methadone 1 (9%), buprenorphine 1 (11%) 20 completed (11 methadone, 9 buprenorphine)</p> <p>Dropouts from treatment: methadone 4 (3 missed doses, 1 elective withdrawal), buprenorphine 6 (1 medical condition, 4 missed doses, 1 elective withdrawal)</p>	No adjusted results published.
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<p>Jones 2010 Multi - centre (USA + Austria)</p>	<p>2005 – 2008</p>	<p>Randomised control trial</p>	<p>175 89 methadone 86 buprenorphine</p>	<p>Multiple centres in North America and Europe</p>	<p>Inclusion: prescription of opioid replacement</p> <p>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.</p>	<p>Total birth weight of offspring: methadone 2878g (SE ± 66.3), buprenorphine 3092g (SE ± 72.6)</p> <p>Total body length of offspring at birth: methadone 47.8cm (SE ± 0.5), buprenorphine 49.8cm (SE ± 0.5)</p> <p>Infant head circumference: methadone 33.0cm (SE ± 0.3), buprenorphine 33.8cm (SE ± 0.3)</p> <p>Prematurity: methadone 14(19%), buprenorphine 4(7%)</p> <p>Gestation age: methadone 37.9weeks (SE ± 0.3), buprenorphine 39.1weeks (SE ± 0.3)</p> <p>Treatment for NAS: methadone 41 (57%), buprenorphine 27 (47%)</p> <p>Duration of hospital stay methadone 17.5days (SE ± 1.5), buprenorphine 10.0days (SE ± 1.2)</p> <p>Foetal 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.</p> <p>Maternal adverse events: methadone 83 (93%) nonserious maternal events, and 14 (16%) serious. Buprenorphine 66 (77%) nonserious maternal events, and 8 (9%) serious.</p> <p>Caesarean section: Methadone 27 (37%) and Buprenorphine 17 (29%)</p> <p>Drop out from treatment: Methadone 16 (voluntary withdraw 10, involuntary 6) buprenorphine 28 (voluntary 26, involuntary 2)</p>	<p>No adjusted results published.</p>
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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	<p>Intra-uterine deaths: methadone 0, buprenorphine 2 (5%)</p> <p>Gestational age at birth: methadone 38.6 weeks (SD ± 1.5), buprenorphine 39.5weeks (SD +- 2.0)</p> <p>Total birth weight of offspring: methadone 2941g (SD ± 483), buprenorphine 3250g (SD ± 528)</p> <p>Total body length at birth: methadone 47.6cm (SD ± 2.2), buprenorphine 48.4cm (SD ±2.5)</p> <p>Head Circumference: methadone 33.8cm (SD ± 1.5), buprenorphine 34.0cm (SD±1.4)</p> <p>Treatment for NAS: methadone 19 (52.8%), buprenorphine 7(14.9%)</p> <p>Length of offspring hospital admission: methadone 19.7days (SD ± 18.8) buprenorphine 9.4days (SD ± 8.4)</p>	No adjusted results published.
Kaltenbach 2019 Multi-centre (North America + Europe)	2005 – 2008	Randomised control trial	Randomised control trial	Multicentre in North America and Europe	Inclusion: Recruited in Jones 2010, with same inclusion criteria. Exclusion: as per Jones 2010.	Offspring development at 3-36months within normal range, no difference between buprenorphine and methadone.	No adjusted results published.

Konijnberg 2015 Norway	2005 – 2007	Prospective Cohort study	66 24 methadone 11 buprenorphine 31 control	Multiple opioid maintenance therapy centres 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 centres, 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 centres 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 analysed as not presentation as distribution not reported).	No adjusted results published.
Myer 2016 USA	2000 - 2012	Retrospective cohort study	609 248 methadone 361 buprenorphine	Single addiction centre in USA	Inclusion: All subjects in the centre between 2000 – 2012 with exposure to methadone or buprenorphine Exclusion: Enrolment in the MOTHER study (Jones 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 <5 th Percentile: methadone 32 (13%), buprenorphine 40 (11%) – not analysed under SGA in meta-analysis due to difference to standard definition of 10 th percentile.	No adjusted results published.

Nechanska 2018 Norway	2004 – 2013	Retrospective cohort study	235 99 methadone 97 buprenorphine	Entire Norwegian population	<p>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).</p> <p>Exclusion: not specified</p>	<p>Total birth weight of offspring: methadone 3268g (SD ± 603), buprenorphine 3333g (SD ± 437)</p> <p>Birth length: methadone 48.7cm (SD ± 3.0), buprenorphine 49.3 (SD ± 2.0)</p> <p>Head circumference: methadone 34.4cm (SD ± 1.5), buprenorphine 34.7cm (SD ± 1.6)</p> <p>Gestational age at birth: methadone 38.9weeks (SD ± 1.9), buprenorphine 39.2weeks (SD ± 2.4)</p> <p>Stillbirths: methadone <4, buprenorphine 0 (incidence recorded as less than 4 due to data-protection legislation)</p> <p>Preterm birth: methadone 9 (9.3%), buprenorphine 5 (5.2%)</p> <p>Small for gestational age at birth: methadone 10 (10.3%), buprenorphine 5 (5.2%)</p> <p>Treatment for NAS: methadone 55 (44.2 – 64.9) buprenorphine 51 (43.2-63.9)</p> <p>Caesarean section: methadone 23 (23.7%), buprenorphine 21 (23.7%)</p>	<p>Adjusted for maternal age, marital status, education, and tobacco smoking during pregnancy published. Buprenorphine compared to methadone, with methadone being the reference group.</p> <p>Preterm birth: Odds Ratio (OR) 0.73 (95% CI: 0.16 to 3.36)</p> <p>Small for gestational age: OR 0.83 (95% CI: 0.22 to 3.20)</p> <p>Treatment for NAS 0.94 (95% CI: 0.46 - 1.92)</p> <p>Linear regression performed for continuous dependant variables. Not analysed 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)</p>
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Nehanska 2018 Czech Republic	2000 - 2014	Retrospective cohort study	333 152 methadone 152 buprenorphine	Entire Czech Republic population	<p>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.</p> <p>Exclusion: not specified.</p>	<p>Total birth weight of offspring: methadone 3017g (SD \pm 476), buprenorphine 3115g (SD \pm 453)</p> <p>Small for gestational age at birth: methadone 19 (12.8%), buprenorphine 21 (13.8%)</p> <p>Birth length: methadone 48.1cm (SD \pm 2.4), buprenorphine 48.6cm (SD \pm 2.3)</p> <p>Head circumference at birth: methadone 33.8cm (SD \pm 1.8) buprenorphine 34.0cm (SD \pm 1.6)</p> <p>Gestational age at birth: methadone 38.3weeks (SD \pm 2.6) buprenorphine 38.5weeks (SD \pm 2.7)</p> <p>Stillbirth: methadone 4 (2.6%) buprenorphine 0 (0%)</p> <p>Preterm births: methadone 25 (16.9%) buprenorphine 25 (16.4%)</p> <p>Caesarean Section: methadone 23 (14.6%), buprenorphine 32 (22.1%)</p> <p>After adjustment for maternal age, marital status, education, and tobacco smoking during pregnancy</p>	<p>Adjusted for maternal age, marital status, education and tobacco smoking during pregnancy published. Buprenorphine compared to methadone, with methadone being the reference group.</p> <p>Preterm birth OR: 0.92 (95% CI 0.48 to 1.74)</p> <p>Small for gestational age at birth OR 1.07 (95% CI: 0.52 to 2.21)</p> <p>Linear regression performed for continuous dependant variables. Not analysed as unable to pool published results.</p> <p>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).</p>
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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 analysed as no comparison to buprenorphine published.

Tolia 2018 USA	2011 – 2014	Retrospective cohort study	3364 2202 methadone 1162 buprenorphine	Pediatrix Clinical Data from neonatal ICUs across the USA (241 centres)	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%) Caesarean 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, caesarean delivery, sex, out born status, type of pharmacotherapy, breast milk use, year and controlled for centre with robust sandwich variances) Not analysed 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). Caesarean delivery HR 0.98 (0.90, 1, 1.07)
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Whitham 2010 Australia	2002 - 2006	Open-label non- randomised flexible- dosing longitudinal study	52 22 methadone 30 buprenorphine	2 specialist drug and alcohol antenatal clinics Adelaide, South Australia.	<p>Inclusion: prescription of methadone or buprenorphine and <28 weeks gestational and mothers aged between 16-40yrs.</p> <p>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 foetal malformations on admission; participation in another clinical research project that interfered with the present study.</p>	<p>Total birth weight of offspring: methadone 2749.09g (SD ± 484.32), buprenorphine 3055.52 (SD ±511.65)</p> <p>Birth length: methadone 46.52cm (SD ±3.21), buprenorphine 47.93 (SD ± 2.54)</p> <p>Head circumference: methadone 32.65cm (SD ± 1.34), buprenorphine 33.7cm (SD ± 1.81)</p> <p>Gestational age at birth: methadone 38.09weeks (SD ± 1.95, buprenorphine 38.73weeks (SD ± 1.95)</p> <p>NAS treatment required: methadone 11(50%), buprenorphine 14 (47%)</p>	<p>Adjustment for age, family income, Marijuana use, and adjustment used for visual studies (not analysed as not relevant outcome for this meta-analysis).</p>
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Wiegand 2015 USA	2011 – 2013	Retrospective cohort study	62 patients (31 methadone, 31 buprenorphine + naloxone)	Single addiction centre Northern Carolina Chapel Hill, USA.	<p>Inclusion: prescription of opioid replacement</p> <p>Exclusion: treatment started less than 30day before delivery, delivery at an outside hospital, multiple gestations, intrauterine fetal demise or still-birth, or an anomalous foetus or new-born and multiple births.</p>	<p>Treatment for NAS: methadone 16 (51%), buprenorphine 8 (21%)</p> <p>Duration of NAS: methadone 11.4days (SD ± 3.4), buprenorphine 10.6 (SD ± 3.1)</p> <p>Head Circumference at birth: methadone 32.9 (SD ± 2.5), buprenorphine 34.4 (SD ± 1.4)</p> <p>Total birth weight of offspring: methadone 2885.9 (SD ± 691.2), buprenorphine 3174g (SD ± 532.8)</p> <p>Total length of offspring at birth: methadone 47.9cm (SD ± 4.0), buprenorphine 50.1 (SD ± 2.5)</p> <p>Preterm: methadone 5(16.1%), buprenorphine 1(19.4%)</p> <p>Length of hospital admission: methadone 9.8days (SD ± 7.4), buprenorphine 5.7 (SD ± 5.0)</p> <p>Caesarean Section: methadone 8 (25.8%), buprenorphine 7 (22.6%)</p>	<p>Adjustment for gestational age and maternal indication for opiates. Buprenorphine compared to methadone, with methadone being the reference group.</p> <p>Treatment for NAS: OR 2.55 (95% CI: 1.31 - 4.98)</p>
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Figure 1: CONSORT flow diagram of studies included in analysis

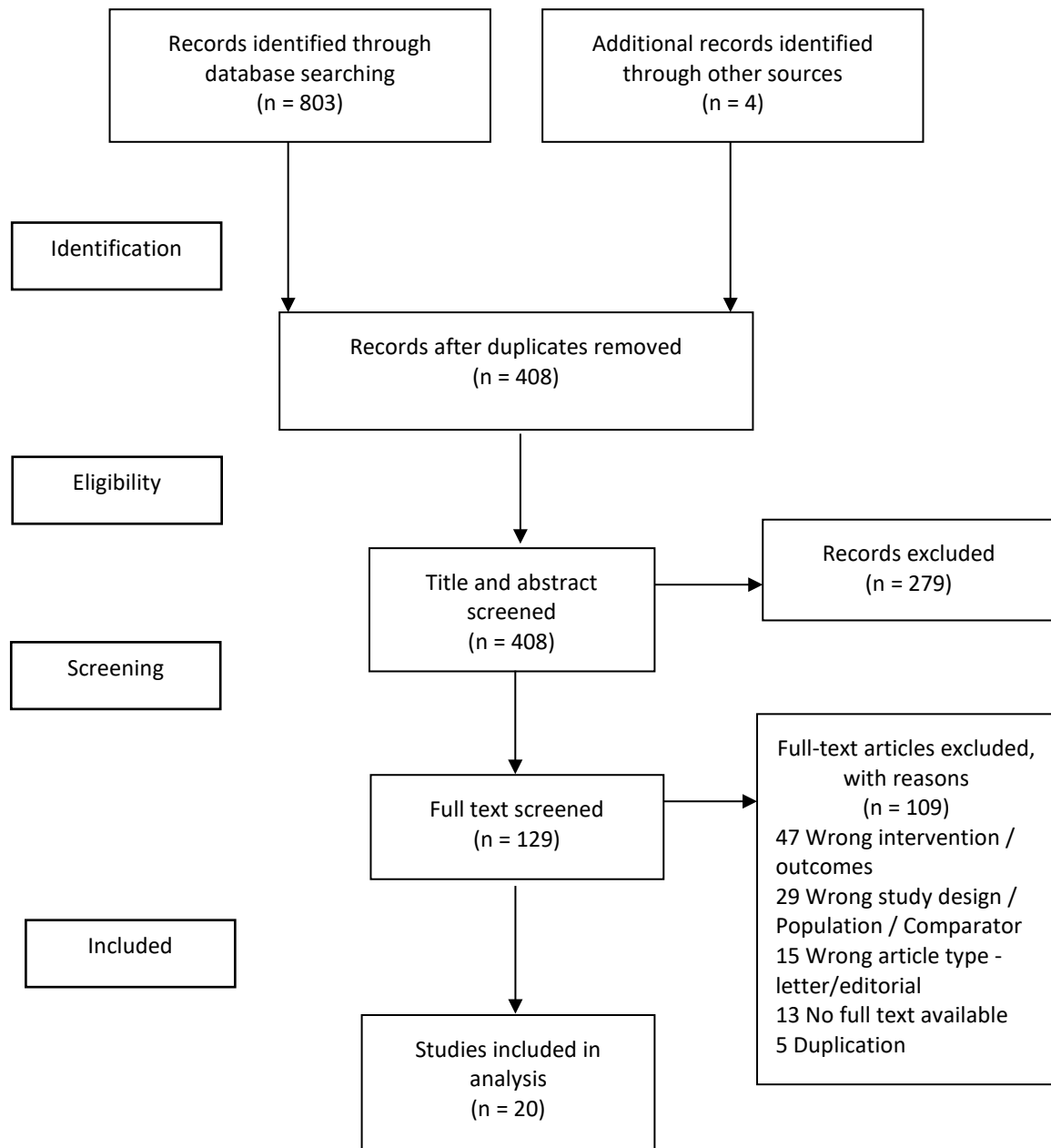


Figure 2. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and weighted mean difference in offspring birth weight (grams)

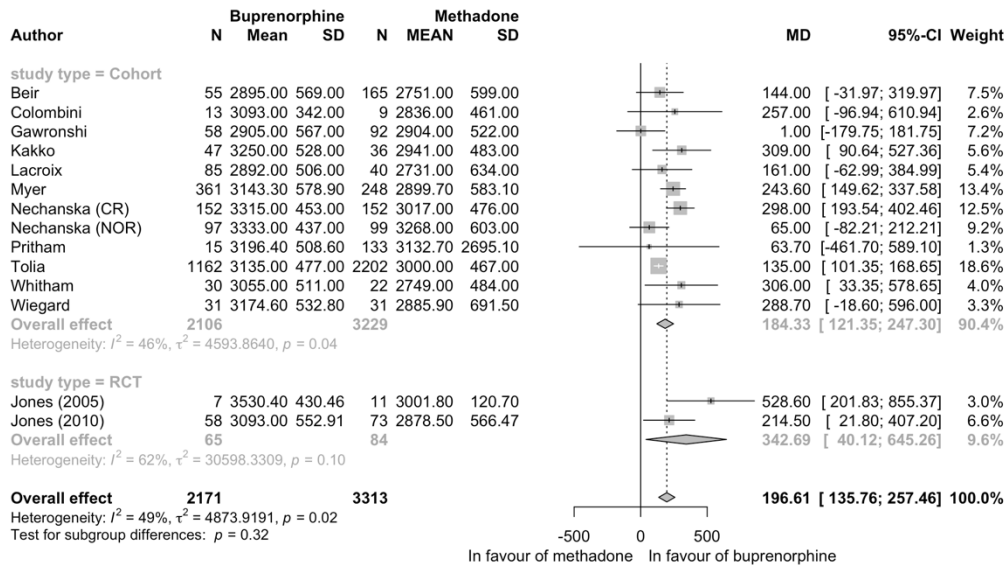


Figure 3. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and weighted mean difference in offspring total body length (centimetres)

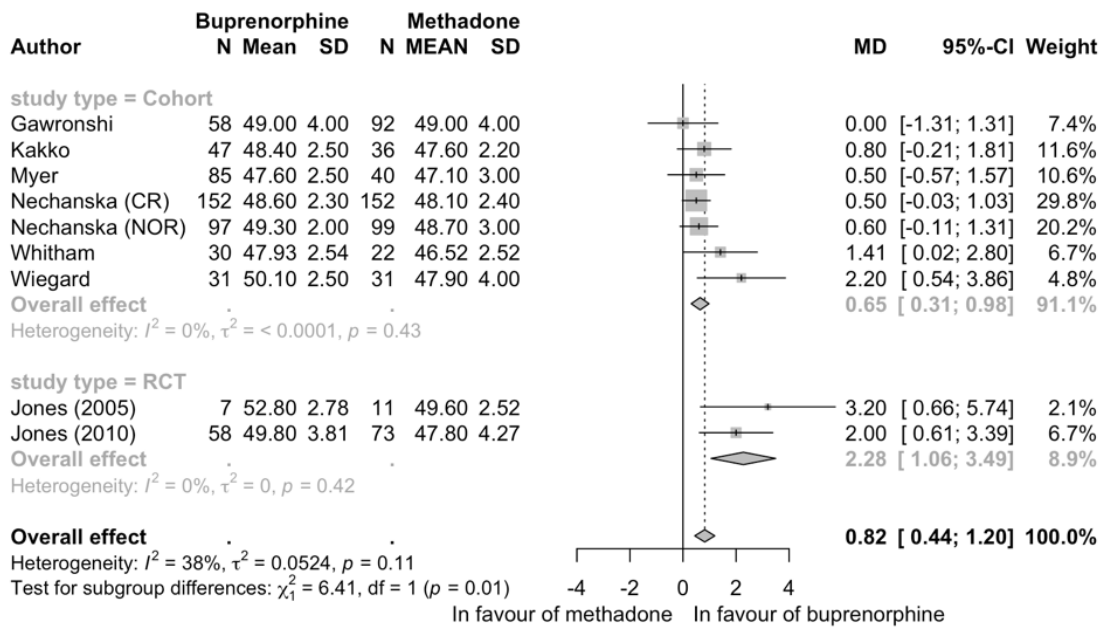


Figure 4 - Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and risk ratio for prematurity

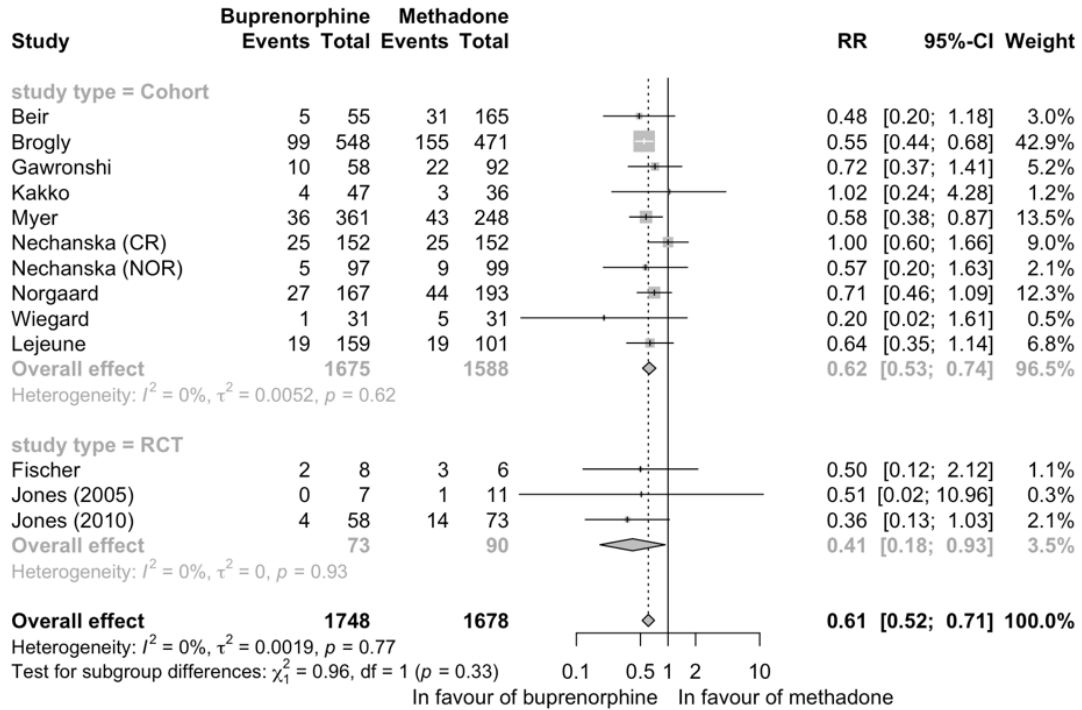


Figure 5. Meta-analysis of exposure to buprenorphine versus methadone during pregnancy and risk ratio for NAS treatment

