



Project

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St. Vincent's Hospital, Melbourne
Australia



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Long-Term Outcomes of Prenatal Exposure to Methadone or Buprenorphine

4 March 2022

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Key Ideas...

The Big Idea... opioid exposure during pregnancy has developmental consequences which is progressive over time.

The Key Clinical Decision... selecting a model of treatment that has the least evidence of harm.

The Key Clinical Skills... to learn how to talk to pregnant women about their substance use non-judgementally.

The Main Scientific Mechanisms... opioid receptors in foetal neurological structures.

The Key Insight for Clinician as a Professional... does my own bias interfere with identifying and treating pregnant women with opioid use disorder?

Opioid Use Disorder and Pregnancy

Prevalence in Australia is difficult to capture.

Amongst pregnant women, 2.4% reported using illicit substances before knowledge of pregnancy. National Drug Strategy

Household Survey (AIHW 2014)

Neonatal Abstinence Syndrome (NAS)

- Aus: ~3 per 1000 live births
- USA: rapidly increasing, baby born every 25 minutes

Opioid Use Disorder and Pregnancy

Maternal opioid use disorder > negative consequences

- maternal death (OR 4.6; 95%CI 1.8 to 12.1)
- intrauterine growth restriction (OR 2.7; 95%CI 2.4 to 2.9)
- preterm labour (OR 2.1; 95%CI 2.0 to 2.3)
- stillbirth (OR 1.5; 95%CI 1.3 to 1.8)

I. Foetal Impact

I. Foetal Impact



Opioid receptors are diffusely present in fetal neurologic structures from a very early gestational age

Opioids (and metabolites) freely cross the placenta

II. Neonatal Impact

II. Neonatal Impact



Neonatal Abstinence Syndrome

**Central and autonomic nervous system &
gastrointestinal system dysfunction**

DATE:	SCORE	TIME
High pitched cry: inconsolable >15 sec. OR intermittently for <5 min.	2	
High pitched cry: inconsolable >15 sec. AND intermittently for ≥5 min.	3	
Sleeps <1 hour after feeding	3	
Sleeps <2 hours after feeding	2	
Sleeps <3 hours after feeding	1	
Hyperactive Moro	1	
Markedly hyperactive Moro	2	
Mild tremors: disturbed	1	
Moderate-severe tremors: disturbed	2	
Mild tremors: undisturbed	1	
Moderate-severe tremors: undisturbed	2	
Increased muscle tone	1-2	
Excoriation (indicate specific area): _____	1-2	
Generalized seizure	8	
Fever ≥37.2°C (99°F)	1	
Frequent yawning (≥4 in an interval)	1	
Sweating	1	
Nasal stuffiness	1	
Sneezing (≥4 in an interval)	1	
Tachypnea (rate >60/min.)	2	
Poor feeding	2	
Vomiting (or regurgitation)	2	
Loose stools	2	
≤90% of birth weight	2	
Excessive irritability	1-3	
Total score		
Initials of scorer		

*“That tremulous,
unsettled,
inconsolable baby
with a high-pitched
cry, red face, arching
back, who is vomiting
and feeding poorly”*


Oral morphine
Phenobarbitol, Clonidine
Average length of stay 17-23 days

III. Developmental Impact

III. Developmental Impact

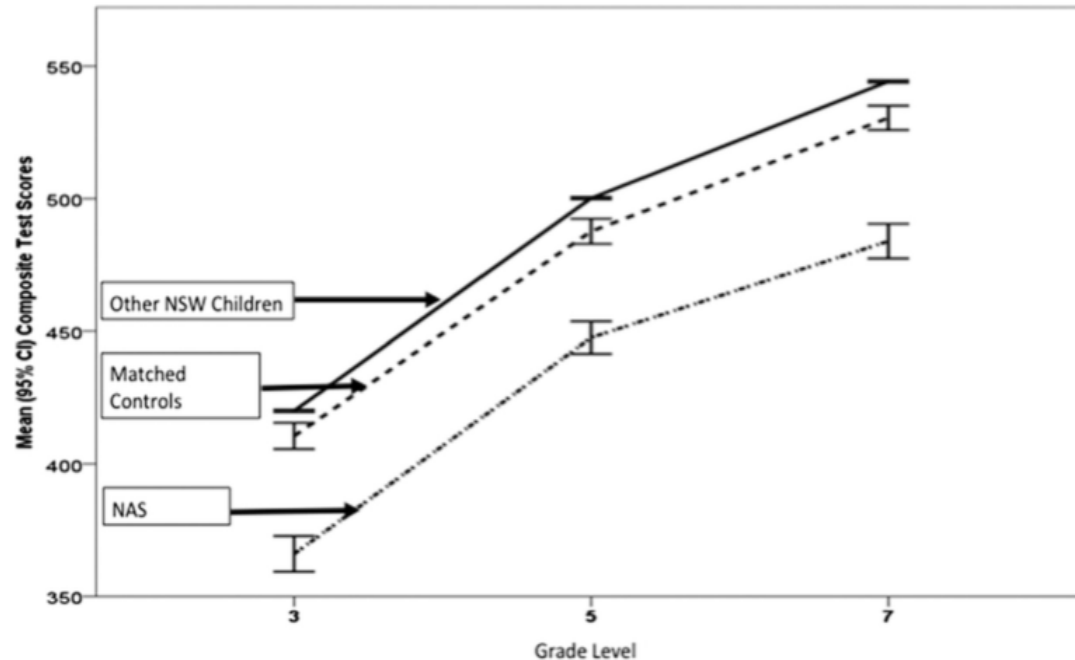


Neonatal Abstinence Syndrome and High School Performance

Ju Lee Oei, MD ; Edward Melhuish, PhD; Hannah Uebel; Nadin Azzam; Courtney Breen, PhD; Lucinda Burns, PhD; Lisa Hilder, MBBS; Barbara Bajuk, MPH; Mohamed E. Abdel-Latif, MD; Meredith Ward, FRACP; John M. Feller, FRACP; Janet Falconer, CNC; Sara Clews, CNC; John Eastwood, FRACP; Annie Li; Ian M. Wright, FRACP

- Data Linkage Study (2000-2006)
 - Perinatal Data Collection
 - Admitted Patient Data
 - NAPLAN database
- 468, 239 children
- Follow-up until Year 7

Neonatal Abstinence Syndrome and High School Performance



NAS is associated with poorer academic performance at every grade and every domain of testing.

Difference was progressive.

Poor school performance increases the risk of myriad of poor adult outcomes.

Treatment of Opioid Use Disorder in Pregnancy

Opioid Maintenance Therapy (OMT) has been the gold standard pharmacological treatment for opioid-dependent pregnant women. >5 decades of experience and substantial literature base supports its benefit.

However...

Despite stabilization of the intrauterine environment through
long-acting OMT

Majority of newborns show symptoms of NAS

&

Long-term neurodevelopmental data is lacking



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Prenatal exposure to methadone or buprenorphine and long-term outcomes: A meta-analysis

Jannike Mørch Andersen^{a,*}, Gudrun Høiseth^{a,b}, Egil Nygaard^c

- Systemic literature search (1946 to 2018)
- 29 studies including 8,097 children
- Mean follow up 3.1 years (range 3 months-11 years)
- Measured cognition, motor function, attention, executive function, behaviour and vision

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Study or Subgroup	Non-user			OMT			Weight	Std. Mean Difference	
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Cognition									
Bauman 1986, 3-6 years	100.4	18.36	70	92.71	15.36	70	1.0%	0.45	[0.12, 0.79]
Bernstein 1984, 4 months	115	14.7	23	109.9	12.8	17	0.8%	0.36	[-0.27, 0.99]
Chasnoff 1986, 12 months	105.8	8.1	27	99.6	10.6	20	0.8%	0.66	[0.07, 1.25]
Chasnoff 1986, 24 months	96.2	15.9	14	98.7	16	16	0.7%	-0.15	[-0.87, 0.57]
Chasnoff 1986, 3 months	99.2	9	34	104.2	11.1	36	0.9%	-0.49	[-0.96, -0.01]
Chasnoff 1986, 6 months	111	12.3	29	103.6	13.5	26	0.9%	0.57	[0.03, 1.11]
Davis 1988, 6-15 years	96.32	8.72	28	89.58	10.32	12	0.7%	0.72	[0.02, 1.41]
Hans 2001, 12 months	109	13.7	45	107	14.3	33	0.9%	0.14	[-0.31, 0.59]
Hans 2001, 18 months	103	13.1	45	95	16.3	33	0.9%	0.55	[0.09, 1.00]
Hans 2001, 24 months	96	12.3	45	92	12.7	33	0.9%	0.32	[-0.13, 0.77]
Hans 2001, 4 months	114	15.1	45	111	12.3	33	0.9%	0.21	[-0.24, 0.66]
Hans 2001, 8 months	120	20.2	45	116	19.5	33	0.9%	0.20	[-0.25, 0.65]
Hunt 2008, 18 months	105.02	23	61	88.2	16.4	79	1.0%	0.86	[0.51, 1.21]
Hunt 2008, 3 years	107.5	13.4	44	99.9	15.1	67	1.0%	0.52	[0.14, 0.91]
Kaltenbach 1979, 12 months	109.4	9.35	27	103.4	9.26	26	0.9%	0.64	[0.08, 1.19]
Kaltenbach 1979, 24 months	94.62	11.93	24	90.88	8.26	17	0.8%	0.35	[-0.28, 0.97]
Kaltenbach 1987, 6 months	104.4	12	63	103.5	12	105	1.0%	0.07	[-0.24, 0.39]
Kaltenbach 1989, 12 months	106.5	6.41	17	102.5	11.38	17	0.8%	0.42	[-0.26, 1.10]
Kaltenbach 1989, 24 months	103.9	11.49	17	100.9	18.04	27	0.8%	0.19	[-0.42, 0.79]
Kaltenbach 1989, 4 years	106.1	13.1	17	106.5	12.96	27	0.8%	-0.03	[-0.64, 0.58]
Kaltenbach 1989, 6 months	105.6	7.31	17	107.9	12.23	27	0.8%	-0.21	[-0.82, 0.40]
Konijnenberg 2015a, 4 years	0.43	0.46	31	0.38	0.58	35	0.9%	0.09	[-0.39, 0.58]
Lifschitz 1985, 3-5 years	89.4	10.8	41	90.4	13	26	0.9%	-0.08	[-0.58, 0.41]
Rosen 1985, 12 months	107	2.8	22	98.4	2.7	41	0.7%	3.11	[2.34, 3.87]
Rosen 1985, 18 months	106.4	3.6	23	96	2.3	38	0.7%	3.60	[2.76, 4.44]
Rosen 1985, 24 months	96.9	3.1	22	90.4	2.6	34	0.8%	2.28	[1.59, 2.98]
Rosen 1985, 3 years	46.3	2.3	21	44.6	2.1	39	0.9%	0.77	[0.22, 1.32]
Rosen 1985, 6 months	100.7	4.2	23	95	2.5	41	0.8%	1.76	[1.16, 2.35]
Rosen 1985, 6 years	88.9	3.2	10	89.22	3.4	18	0.7%	-0.09	[-0.87, 0.68]
Salo 2009, 3 years	105.4	1.26	13	8.91	0.73	21	0.7%	1.65	[0.84, 2.46]
Salo 2010, 7 months	105.11	7.61	57	92.33	10.73	15	0.8%	1.52	[0.89, 2.14]
Strauss 1976, 12 months	114.8	11.3	26	113.4	10.2	25	0.9%	0.13	[-0.42, 0.68]
Strauss 1976, 3 months	115.3	13.5	26	112.5	11.5	25	0.9%	0.22	[-0.33, 0.77]
Strauss 1976, 6 months	114.3	20.9	26	115.7	16.8	25	0.9%	-0.07	[-0.62, 0.48]
Strauss 1979, 5 years	86.2	16.2	30	86.8	13.3	33	0.9%	-0.04	[-0.53, 0.45]
van Baar 1990, 12 months	114	17	34	108	12	26	0.9%	0.39	[-0.12, 0.91]
van Baar 1990, 18 months	99	19	34	92	14	22	0.9%	0.40	[-0.14, 0.94]
van Baar 1990, 24 months	98	16	34	86	15	26	0.9%	0.76	[0.23, 1.29]
van Baar 1990, 30 months	101	20	34	87	18	25	0.9%	0.72	[0.19, 1.25]
van Baar 1990, 6 months	107	13	37	106	13	27	0.9%	0.08	[-0.42, 0.57]
van Baar 1994, 3 1/2 years	109	11	32	99	9	23	0.8%	0.96	[0.40, 1.53]
van Baar 1994, 4 1/2 years	103	15	31	85	11	23	0.8%	1.32	[0.72, 1.92]
van Baar 1994, 5 1/2 years	102	17	30	90	12	22	0.8%	0.78	[0.21, 1.35]
Wilson 1981, 9 months	105.5	15.6	55	99.3	15.5	35	0.9%	0.40	[-0.03, 0.82]
Wilson 1989, 18 months	97.4	14.4	42	92	14.5	29	0.9%	0.37	[-0.11, 0.85]
Wilson 1989, 24 months	90.2	14.6	48	88.8	15.5	32	0.9%	0.09	[-0.35, 0.54]
Subtotal (95% CI)			1519			1460	39.1%	0.56	[0.38, 0.74]

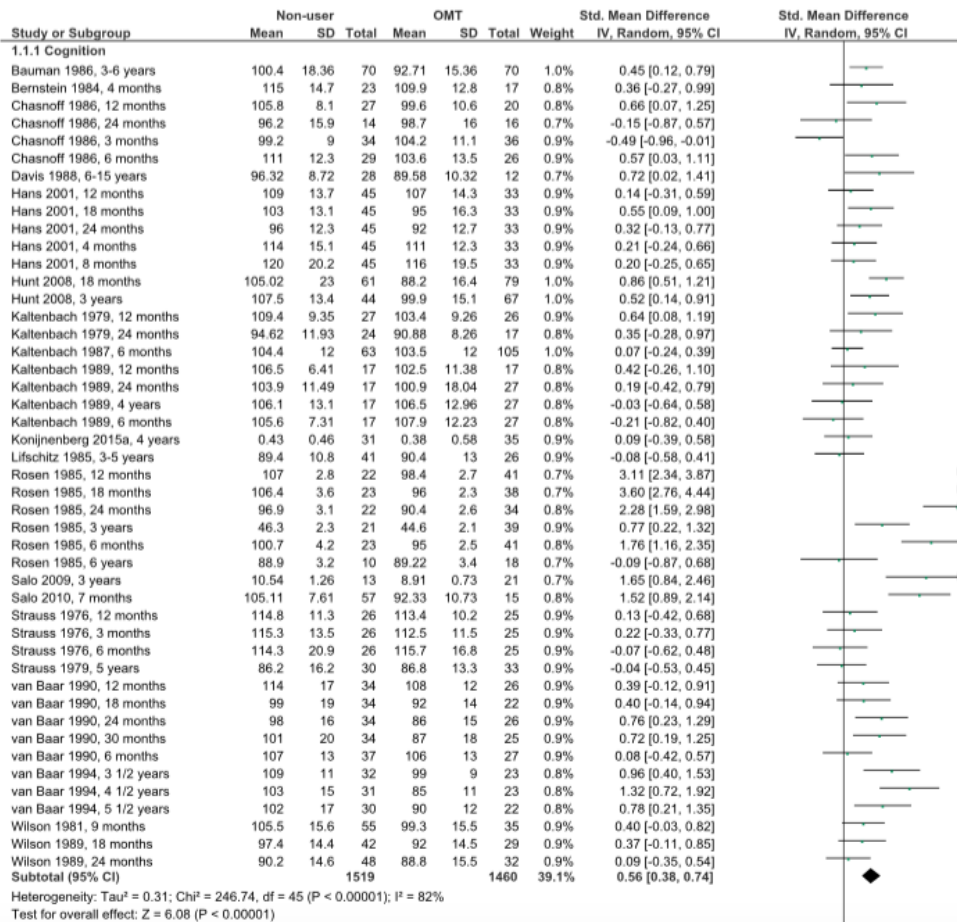
Heterogeneity: Tau² = 0.31; Chi² = 246.74, df = 45 (P < 0.00001); I² = 82%
 Test for overall effect: Z = 6.08 (P < 0.00001)

← Favours OMT Favours non-exposed →

Prenatal exposure to methadone or buprenorphine and long-term outcomes: A meta-analysis

A

Jannike Mørch Andersen^{a,*}, Gudrun Høiseth^{a,b}, Egil Nygaard^c



OMT vs Non-exposed

OMT group had worse developmental outcomes than non-exposed group.

Effect size was small (0.49) but statistically significant ($p < 0.00001$).

Practically translates into a 7-point IQ difference.

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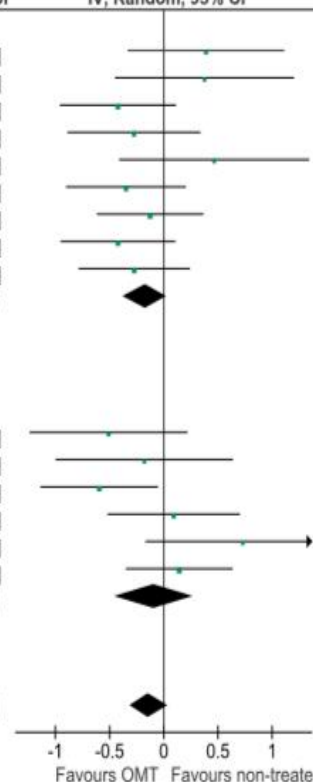
Jannike Mørch Andersen^{a,*}, Gudrun Høiseth^{a,b}, Egil Nygaard^c

Study or Subgroup	Untreated			OMT			Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
2.1.1 Cognition									
Chasnoff 1986, 12 months	103.5	8.1	12	99.6	10.6	20	5.2%	0.39 [-0.33, 1.11]	
Chasnoff 1986, 24 months	104.8	15.1	9	98.7	16	16	4.1%	0.38 [-0.45, 1.20]	
Chasnoff 1986, 3 months	99	13.6	22	104.2	11.1	36	8.3%	-0.42 [-0.96, 0.11]	
Chasnoff 1986, 6 months	99.9	12.7	17	103.6	13.5	26	6.8%	-0.28 [-0.89, 0.34]	
Davis 1988, 6-15 years	95.11	12.8	9	89.58	10.32	12	3.7%	0.46 [-0.41, 1.34]	
Lifschitz 1985, 3-5 years	85.3	15.7	25	90.4	13	26	7.9%	-0.35 [-0.90, 0.20]	
Wilson 1981, 9 months	97.2	17.6	29	99.3	15.5	35	9.4%	-0.13 [-0.62, 0.37]	
Wilson 1989, 18 months	86.5	10.7	27	92	14.5	29	8.5%	-0.42 [-0.95, 0.11]	
Wilson 1989, 24 months	84.4	16.4	27	88.8	15.5	32	8.8%	-0.27 [-0.79, 0.24]	
Subtotal (95% CI)			177			232	62.7%	-0.17 [-0.38, 0.03]	
Heterogeneity: Tau ² = 0.00; Chi ² = 8.42, df = 8 (P = 0.39); I ² = 5%									
Test for overall effect: Z = 1.66 (P = 0.10)									
2.1.2 Psychomotor tests									
Chasnoff 1986, 12 months	98.1	12.3	12	104.4	11.9	20	5.1%	-0.51 [-1.24, 0.22]	
Chasnoff 1986, 24 months	97.9	10.1	9	100.3	14.2	16	4.2%	-0.18 [-1.00, 0.64]	
Chasnoff 1986, 3 months	97.6	9.8	22	104.3	11.8	36	8.2%	-0.60 [-1.14, -0.05]	
Chasnoff 1986, 6 months	103.2	8.8	17	102.2	11.9	26	6.8%	0.09 [-0.52, 0.70]	
Davis 1988, 6-15 years	14.17	5.44	12	10.19	4.96	9	3.5%	0.73 [-0.17, 1.63]	
Wilson 1981, 9 months	92.2	19.2	29	89.9	12.6	35	9.4%	0.14 [-0.35, 0.64]	
Subtotal (95% CI)			101			142	37.3%	-0.09 [-0.45, 0.27]	
Heterogeneity: Tau ² = 0.09; Chi ² = 9.04, df = 5 (P = 0.11); I ² = 45%									
Test for overall effect: Z = 0.49 (P = 0.62)									
Total (95% CI)			278			374	100.0%	-0.14 [-0.32, 0.04]	
Heterogeneity: Tau ² = 0.03; Chi ² = 17.66, df = 14 (P = 0.22); I ² = 21%									
Test for overall effect: Z = 1.50 (P = 0.13)									
Test for subgroup differences: Chi ² = 0.15, df = 1 (P = 0.70), I ² = 0%									

OMT vs Untreated

OMT group fared better than the untreated group (untreated heroin or polysubstance use).

Difference in cognitive abilities was on the border of statistical significance (p = 0.10).



← Favours OMT Favours untreated →

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Limitations

OMT and non-exposed groups were poorly matched
> overestimation of difference

High risk of bias in most studies
> researchers not blinded
> attrition bias

Heterogeneity

Lack of studies of older children
> underestimation of long-term difference

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Authors' Conclusion

Mother in OMT is better for the child than a mother with untreated opioid addiction.

'However, potential worse outcomes in the OMT children compared to the non-exposed children emphasize the need to discuss whether OMT should continue to be the only preferred treatment during pregnancy or whether controlled tapering combined with psychosocial treatment should be recommended as an alternative, at least for motivated patients'

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Key Ideas...

The Big Idea... opioid exposure during pregnancy has developmental consequences which is progressive over time.

The Key Clinical Decision... selecting a model of treatment that has the least evidence of harm.

The Key Clinical Skills... to learn how to talk to pregnant women about their substance use non-judgementally.

The Main Scientific Mechanisms... opioid receptors in foetal neurological structures.

The Key Insight for Clinician as a Professional... does my own bias interfere with identifying and treating pregnant women with substance use disorder?

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1.1.2 Psychomotor tests

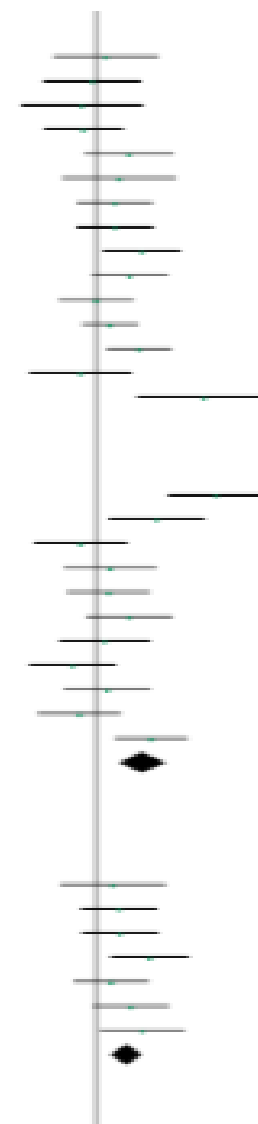
Bernstein 1984, 4 months	118	10.6	23	116.5	15.1	17	0.8%	0.12 [-0.51, 0.74]
Chasnoff 1986, 12 months	103.8	12.5	27	104.4	11.9	20	0.8%	-0.05 [-0.63, 0.53]
Chasnoff 1986, 24 months	98.2	8.9	14	100.3	14.2	16	0.7%	-0.17 [-0.89, 0.55]
Chasnoff 1986, 3 months	102.8	7	34	104.3	11.8	36	0.9%	-0.15 [-0.62, 0.32]
Chasnoff 1986, 6 months	107.6	15.1	29	102.2	11.9	26	0.9%	0.39 [-0.15, 0.92]
Davis 1988, 6-15 years	0.56	0.83	12	0.33	0.82	28	0.8%	0.27 [-0.41, 0.96]
Hans 2001, 12 months	110	17.7	45	106	18	33	0.9%	0.22 [-0.23, 0.67]
Hans 2001, 18 months	109	17.8	45	105	17.6	33	0.9%	0.22 [-0.23, 0.67]
Hans 2001, 24 months	108	14.9	45	100	14.2	33	0.9%	0.54 [0.08, 1.00]
Hans 2001, 4 months	121	12.3	45	116	12.5	33	0.9%	0.40 [-0.06, 0.86]
Hans 2001, 8 months	111	12.4	45	111	12.4	33	0.9%	0.00 [-0.45, 0.45]
Hunt 2008, 18 months	110.13	14.7	61	107.5	16.8	79	1.0%	0.16 [-0.17, 0.50]
Hunt 2008, 3 years	53.9	8.3	44	48.5	8.7	67	1.0%	0.51 [0.12, 0.90]
Kaltenbach 1989, 4 years	50.44	12	17	52.29	8.1	27	0.8%	-0.19 [-0.79, 0.42]
Konijnenberg 2013, 4 years	7.33	2.55	15	4.2	2.18	15	0.7%	1.28 [0.49, 2.08]
Rosen 1985, 12 months	102.8	2.3	22	94.9	2.5	41	0.7%	3.21 [2.43, 3.98]
Rosen 1985, 18 months	105.3	2.2	23	92.6	2.4	38	0.5%	5.39 [4.27, 6.50]
Rosen 1985, 24 months	108	2.7	22	99.1	2.7	34	0.7%	3.25 [2.43, 4.07]
Rosen 1985, 6 months	105.1	2.9	23	101	2.8	41	0.8%	1.43 [0.86, 2.00]
Strauss 1976, 12 months	110.4	9.8	26	102.8	11	25	0.8%	0.72 [0.15, 1.29]
Strauss 1976, 3 months	117.1	14.5	26	119.4	9.1	25	0.9%	-0.19 [-0.74, 0.36]
Strauss 1976, 6 months	111.7	14.5	26	109.4	12.2	25	0.9%	0.17 [-0.38, 0.72]
Strauss 1979, 5 years	48	10.7	30	44.5	9.3	33	0.9%	0.15 [-0.35, 0.64]
van Baar 1990, 12 months	119	20	34	111	20	26	0.9%	0.39 [-0.12, 0.91]
van Baar 1990, 18 months	112	19	33	110	19	22	0.9%	0.10 [-0.44, 0.64]
van Baar 1990, 24 months	100	18	34	105	17	26	0.9%	-0.28 [-0.79, 0.23]
van Baar 1990, 30 months	101	24	34	98	19	25	0.9%	0.13 [-0.38, 0.66]
van Baar 1990, 6 months	114	21	37	118	18	27	0.9%	-0.20 [-0.70, 0.30]
Wilson 1981, 9 months	99	14.5	55	89.9	12.6	35	0.9%	0.65 [0.22, 1.09]
Subtotal (95% CI)			926			919	24.4%	0.56 [0.28, 0.85]

Heterogeneity: $\tau^2 = 0.52$; $\text{Chi}^2 = 234.31$, $\text{df} = 28$ ($P < 0.00001$); $I^2 = 88\%$
 Test for overall effect: $Z = 3.87$ ($P = 0.0001$)

1.1.3 Motor activity observed

Bernstein 1984, 4 months	22.3	2.3	17	18.1	27	23	0.8%	0.20 [-0.43, 0.83]
Hans 2001, 12 months	5.8	1.2	45	5.5	0.9	33	0.9%	0.27 [-0.18, 0.73]
Hans 2001, 18 months	5.7	1	45	5.4	1.1	33	0.9%	0.28 [-0.17, 0.74]
Hans 2001, 24 months	5.5	1.2	45	4.7	1.3	33	0.9%	0.64 [0.18, 1.10]
Hans 2001, 4 months	6	1.1	45	5.8	1.1	33	0.9%	0.18 [-0.27, 0.63]
Hans 2001, 8 months	6.1	1.2	45	5.6	1.2	33	0.9%	0.41 [-0.04, 0.87]
Strauss 1979, 5 years	3	0.8	33	2.5	1	30	0.9%	0.55 [0.04, 1.06]
Subtotal (95% CI)			275			218	6.3%	0.37 [0.19, 0.55]

Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 3.08$, $\text{df} = 6$ ($P = 0.80$); $I^2 = 0\%$
 Test for overall effect: $Z = 3.99$ ($P < 0.0001$)



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1.1.4 Behavior

Davis 1988, 6-15 years	14.17	5.44	12	8.01	3.2	38	0.7%	1.52 [0.76, 2.28]
Hans 2001, 12 months	8.6	1.3	45	8.6	1.7	33	0.9%	0.00 [-0.45, 0.45]
Hans 2001, 18 months	8.9	1.5	45	8.9	1.8	33	0.9%	0.00 [-0.45, 0.45]
Hans 2001, 24 months	9.2	1.5	45	8.7	1.7	33	0.9%	0.31 [-0.14, 0.76]
Hans 2001, 4 months	7.9	1.8	45	7	1.4	33	0.9%	0.54 [0.08, 1.00]
Hans 2001, 8 months	8.4	1.8	45	8.1	1.5	33	0.9%	0.18 [-0.27, 0.63]
Hunt 2008, 18 months	119.15	17.5	61	113.2	15.6	79	1.0%	0.36 [0.02, 0.70]
Hunt 2008, 3 years	46.1	7.7	44	38.4	8.1	67	1.0%	0.96 [0.56, 1.36]
Levine 2018, 4 1/2 years	10.25	5.51	87	5.56	4.12	103	1.0%	0.97 [0.67, 1.27]
Salo 2009, 3 years	11.08	2.59	13	8.57	1.51	21	0.7%	1.23 [0.48, 1.99]
Sarli 2009, 3 months	14.1	1.6	36	14	1.6	35	0.9%	0.06 [-0.40, 0.53]
Strauss 1979, 5 years	3.4	0.9	33	2.8	1.1	30	0.9%	0.59 [0.09, 1.10]
Subtotal (95% CI)			511			528	10.8%	0.52 [0.27, 0.77]

Heterogeneity: $\text{Tau}^2 = 0.14$; $\text{Chi}^2 = 41.28$, $\text{df} = 11$ ($P < 0.0001$); $I^2 = 73\%$

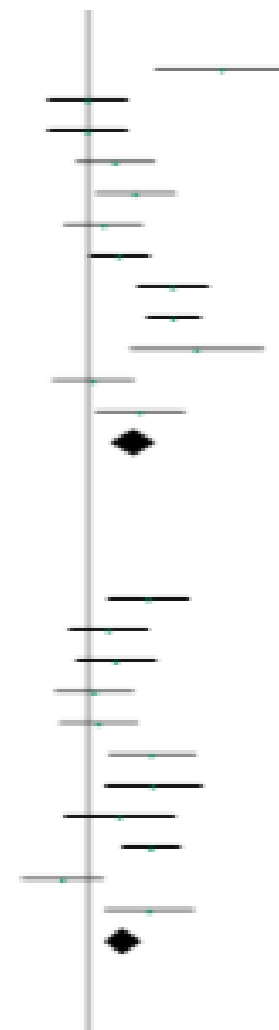
Test for overall effect: $Z = 4.03$ ($P < 0.0001$)

1.1.5 Attention and executive functioning

Hans 2001, 12 months	18.2	2.7	45	16.3	2.8	33	0.9%	0.89 [0.22, 1.15]
Hans 2001, 18 months	17.4	2.5	45	16.6	2.5	33	0.9%	0.24 [-0.21, 0.69]
Hans 2001, 24 months	17.4	2.5	45	16.5	3.1	33	0.9%	0.32 [-0.13, 0.77]
Hans 2001, 4 months	13.1	4.2	45	12.8	3.9	33	0.9%	0.07 [-0.38, 0.52]
Hans 2001, 8 months	18	2.6	45	17.7	2.1	33	0.9%	0.12 [-0.33, 0.57]
Konijnenberg 2015a, 4 years	55.94	12.06	35	47.94	9.37	31	0.9%	0.73 [0.23, 1.23]
Konijnenberg 2015b, 4 years	53.42	4.69	31	50.64	1.8	25	0.9%	0.74 [0.20, 1.29]
Konijnenberg 2018, 11 years	41	42.5	19	26.03	38.5	21	0.8%	0.36 [-0.26, 0.99]
Levine 2018, 2 years	8.44	2.86	88	7.34	2.97	68	1.0%	0.72 [0.38, 1.06]
Schneider 1996, 2 years	0.31	0.13	44	0.35	0.15	30	0.9%	-0.29 [-0.75, 0.18]
Strauss 1979, 5 years	5.3	1.7	33	4.1	1.7	30	0.9%	0.70 [0.19, 1.21]
Subtotal (95% CI)			475			370	9.9%	0.40 [0.19, 0.61]

Heterogeneity: $\text{Tau}^2 = 0.07$; $\text{Chi}^2 = 21.97$, $\text{df} = 10$ ($P = 0.02$); $I^2 = 54\%$

Test for overall effect: $Z = 3.75$ ($P = 0.0002$)



Prenatal exposure to methadone or buprenorphine and long-term outcomes: A meta-analysis

A

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1.1.6 Vision

Konijnenberg 2013, 4 years	181.47	228.65	15	-37.73	208.56	15	0.7%	0.97 [0.21, 1.74]
Konijnenberg 2015b, 4 years	23.5	45.5	25	-6.84	86.41	31	0.9%	0.42 [-0.11, 0.95]
Melinder 2013, 4 years, 13.2"/sec	79.49	11.18	23	77.84	12.2	26	0.8%	0.14 [-0.42, 0.70]
Melinder 2013, 4 years, 6.8"/sec	69.77	13.6	23	59.65	15.07	26	0.8%	0.69 [0.11, 1.27]
Whitham 2010, 4 months, bupr., 48'	124.97	16.08	30	124.34	12.35	33	0.9%	0.04 [-0.45, 0.54]
Whitham 2010, 4 months, bupr., 69'	121.02	11.74	30	119.92	11.74	33	0.9%	0.09 [-0.40, 0.59]
Whitham 2010, 4 months, meth., 48'	136.25	18.02	22	124.34	12.35	33	0.8%	0.79 [0.23, 1.35]
Whitham 2010, 4 months, meth., 69'	134.99	33.46	22	119.92	11.74	33	0.9%	0.65 [0.09, 1.20]
Whitham 2015, 3 years, bupr., 48'	103.2	3.3	11	104.7	3.1	15	0.7%	-0.46 [-1.25, 0.33]
Whitham 2015, 3 years, bupr., 69'	102.2	4.5	11	102.7	4.2	15	0.7%	-0.11 [-0.89, 0.67]
Whitham 2015, 3 years, meth., 48'	103.7	3.4	10	104.7	3.1	15	0.7%	-0.30 [-1.11, 0.51]
Whitham 2015, 3 years, meth., 69'	101.1	3.9	10	102.7	4.2	15	0.7%	-0.38 [-1.19, 0.43]
Subtotal (95% CI)			232			290	9.5%	0.25 [0.01, 0.50]

Heterogeneity: $\tau^2 = 0.09$; $\text{Chi}^2 = 20.79$, $\text{df} = 11$ ($P = 0.04$); $I^2 = 47\%$

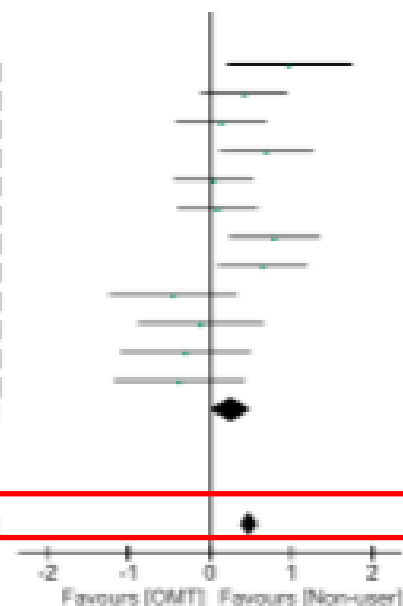
Test for overall effect: $Z = 2.02$ ($P = 0.04$)

Total (95% CI)	3938	3785	100.0%	0.49 [0.38, 0.59]
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Heterogeneity: $\tau^2 = 0.28$; $\text{Chi}^2 = 575.70$, $\text{df} = 116$ ($P < 0.00001$); $I^2 = 80\%$

Test for overall effect: $Z = 9.01$ ($P < 0.00001$)

Test for subgroup differences: $\text{Chi}^2 = 5.77$, $\text{df} = 5$ ($P = 0.33$), $I^2 = 13.4\%$



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Systemic Search for Experimental Animal Studies

29 studies.

Pregnant rats administered methadone/buprenorphine via oral / injection / mini-pump.

Follow up 21 days 5 months (adolescence = 50 days)

- 4 studies showed impaired learning or memory
- 2 studies showed increased likelihood of addiction in adolescents
- 1 study showed impaired social interaction

Inconsistent findings; unable to draw conclusions.