

Supplemental File G

GRADE Ratings and meta-analyses structural neurodevelopmental outcomes

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Summary of available outcomes for head circumference

Head circumference			
Study Type	Outcome	Data	# of studies
Exposure Studies (light, moderate, heavy, very heavy, any level, confirmed-unquantifiable)	Head Circumference at Birth $\leq 10^{\text{th}}$ percentile	aOR and 95% CIs or number of cases with event (grouped together for unadj OR)	2 studies: 1 light, 1 moderate, 0 heavy, 1 very heavy, 0 any, 0 confirmed-unquantifiable
	Head Circumference at Birth $\leq 3^{\text{rd}}$ percentile	aOR and 95% CIs or number of cases with event (grouped together for unadj OR)	1 study: 0 light, 0 moderate, 0 heavy, 0 very heavy, 1 any, 0 confirmed-unquantifiable
	Head Circumference Percentile at Birth	Mean and SDs	3 studies: 1 light, 1 moderate, 1 heavy, 2 very heavy, 0 any, 0 confirmed-unquantifiable
Exposure Studies (light, moderate, heavy, very heavy, any level, confirmed-unquantifiable)	Head Circumference at Birth	Mean and SDs; median and inter-quartile range	16 studies: 1 light, 4 moderate, 7 heavy, 2 very heavy, 1 any, 3 confirmed-unquantifiable
	Postnatal Head Circumference $\leq 10^{\text{th}}$ percentile	aOR and 95% CIs or number of cases with event (grouped together for unadj OR)	8 studies: 1 light, 2 moderate, 1 heavy, 2 very heavy, 0 any, 42 confirmed-unquantifiable
	Postnatal Head Circumference >12 months of age	Mean and SDs	8 studies: 1 light, 0 moderate, 2 heavy, 1 very heavy, 0 any, 4 confirmed-unquantifiable
	Postnatal Head Circumference Percentile	Mean and SDs	1 study: 1 heavy
Diagnosed Studies (FASD, FAS, pFAS, Other FASDs) (3yrs – 22 yrs)	Head Circumference at Birth	Mean and SDs	4 studies: 0 FASD, 0 FAS, 3 pFAS, 3 Other
	Postnatal Head Circumference (6-9 yrs)	Mean and SDs	14 studies: 4 FASD, 7 FAS, 5 pFAS, 3 Other
	Postnatal Head Circumference (9-18 yrs)	Mean and SDs	4 studies: 1 FASD, 2 FAS, 2 pFAS, 4 Other
	Postnatal Head Circumference Centiles	Mean and SDs	9 studies: 0 FASD, 6 FAS, 8 pFAS, 7 Other
	Postnatal Head Circumference $\leq 3^{\text{rd}}$ percentile	% or number of cases with event (grouped together for unadj OR)	6 studies: 1 FASD, 4 FAS, 4 pFAS, 4 Other
	Postnatal Head Circumference $\leq 10^{\text{th}}$ percentile	% or number of cases with event (grouped together for unadj OR)	8 studies: 2 FASD, 6 FAS, 5 pFAS, 6 Other

GRADE ratings for head circumference

	Certainty assessment					No of patients		Effect		Certainty
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Birth Head Circumference <10 th Percentile										
Light prenatal alcohol exposure (1-20g/w in at least one trimester)										
1	not serious	not serious	not serious	serious ^d	none	NR	NR ^g	OR 0.99 (0.52 to 1.88)	-	⊕⊕⊕○ Moderate
Moderate prenatal alcohol exposure (21-100g/w in at least one trimester)										
1	not serious	not serious	not serious	serious ^d	none	NR	NR ^g	OR 0.79 (0.19 to 3.29)	-	⊕⊕⊕○ Moderate
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester) – no studies										
Very heavy prenatal alcohol exposure (201g+/w in at least one trimester)										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	111	350	OR 55.43 (3.15 to 975.09)	-	⊕⊕○○ Low
Any Level, Confirmed-Level Unquantifiable – no studies										
Birth Head Circumference <3 rd Percentile										
Any Level of Prenatal Alcohol Exposure										
1	serious ^a	not serious	not serious	serious ^{d,f}	none	872	452	OR 0.71 (0.41 to 1.23)	-	⊕⊕○○ Low
Light, Moderate, Heavy, Very Heavy, Confirmed-Unquantifiable – no studies										
Birth Head Circumference Percentile										
Light prenatal alcohol exposure (1-20g/w in at least one trimester)										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	96	277	-	MD 0.70 lower (6.67 lower to 5.27 higher)	⊕○○○ Very Low
Moderate prenatal alcohol exposure (21-100g/w in at least one trimester)										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	23	277	-	MD 1.90 lower (13.91 lower to 10.11 higher)	⊕○○○ Very Low
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	33	47	-	MD 5.80 higher (3.87 lower to 15.47 higher)	⊕○○○ Very Low
Very heavy prenatal alcohol exposure (201g+/w in at least one trimester)										
2	serious ^a	not serious	serious ^c	serious ^f	none	35	286	-	MD 11.97 lower (23.42 lower to 0.52 lower)	⊕○○○ Very Low
Any Level, Confirmed-Unquantifiable – no studies										
Birth Head Circumference (cm)										
Light prenatal alcohol exposure (1-20g/w in at least one trimester)										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	112	97	-	MD 0.00 (0.35 lower to 0.35 higher)	⊕○○○ Very Low
Moderate prenatal alcohol exposure (21-100g/w in at least one trimester)										
4	serious ^a	not serious	not serious	not serious	none	2188	144614	-	MD 0.19 lower (0.28 lower to 0.11 lower)	⊕⊕⊕○ Moderate
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)										

7	serious ^a	not serious	serious ^c	not serious	none	295	1709	-	MD 0.78 lower (1.38 lower to 0.19 lower)	⊕⊕○○ Low
Very heavy prenatal alcohol exposure (201g+/w in at least one trimester)										
2	serious ^a	not serious	not serious	serious ^f	none	52	101	-	MD 1.90 lower (2.81 lower to 0.99 lower)	⊕⊕○○ Low
Any prenatal alcohol exposure (level dichotomised to yes/no)										
1	serious ^a	not serious	not serious	serious ^{d,f}	none	28	28	-	MD 0.10 lower (0.71 lower to 0.91 higher)	⊕⊕○○ Low
Confirmed prenatal alcohol exposure-level unquantifiable (quasi heavy/very heavy)										
3	serious ^a	not serious	not serious	serious ^f	none	146	93	-	MD 0.85 lower (1.34 lower to 0.36 lower)	⊕⊕○○ Low
Postnatal Head Circumference (<10 th percentile)										
Light prenatal alcohol exposure (1-20g/w in at least one trimester)										
1	not serious	not serious	not serious	serious ^d	none	NR	NR ^g	OR 0.81 (0.48 to 1.37)	-	⊕⊕⊕○ Moderate
Moderate prenatal alcohol exposure (21-100g/w in at least one trimester)										
2	not serious	not serious	not serious	not serious	none	NR	NR ^{g,h}	OR 1.94 (1.04 to 3.62)	-	⊕⊕⊕⊕ High
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	14	26	OR 91.54 (4.61 to 1817.39)	-	⊕⊕○○ Low
Very heavy prenatal alcohol exposure (201g+/w in at least one trimester)										
2	serious ^a	serious ^b	serious ^c	serious ^{e,f}	none	111	350	OR 4.34 (1.71 to 11.06)	-	⊕○○○ Very Low
Any prenatal alcohol exposure (level dichotomised to yes/no) – no studies										
Confirmed prenatal alcohol exposure-Level Unquantifiable										
4	serious ^a	not serious	not serious	serious ^{e,f}	none	449	430	OR 10.55 (6.51 to 17.09)	-	⊕⊕○○ Low
Postnatal Head Circumference > 12months (cm)										
Light prenatal alcohol exposure (1-20g/w in at least one trimester)										
1	serious ^a	not serious	serious ^c	serious ^f	none	112	97	-	MD 2.00 lower (2.31 lower to 1.69 lower)	⊕○○○ Very Low
Moderate prenatal alcohol exposure (21-100g/w in at least one trimester) – no studies										
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)										
2	serious ^a	not serious	serious ^c	serious ^{e,f}	none	110	111	-	MD 1.42 lower (2.15 lower to 0.68 lower)	⊕○○○ Very Low
Very Heavy prenatal alcohol exposure (201g+/w in at least one trimester)										
1	serious ^a	not serious	not serious	serious ^{d,f}	none	22	21	-	MD 0.45 lower (1.28 lower to 0.38 higher)	⊕⊕○○ Low
Any prenatal alcohol exposure (level dichotomised to yes/no) – no studies										
Confirmed prenatal alcohol exposure-Level Unquantifiable										
4	serious ^a	serious ^b	not serious	serious ^f	none	86	121	-	MD 1.21 lower (2.40 lower to 0.02 lower)	⊕○○○ Very Low
Postnatal Head Circumference Percentile										

Light, Moderate, Very Heavy, Any Level, Confirmed-Unquantifiable – no studies										
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	30	44	-	MD 2.40 higher (13.82 lower to 18.62 higher)	⊕○○○ Very Low
DIAGNOSED STUDIES										
Birth Head Circumference (cm)										
FASD, FAS - NA										
pFAS (pFAS or pFAS/FAS or dysmorphic)										
3	serious ^a	serious ^b	serious ^c	not serious	none	152	398	-	MD 1.07 lower (2.15 lower to 0)	⊕○○○ Very Low
Other (ARND, ND-AE, SE-AE, Non-syndromal)										
3	serious ^a	serious ^b	serious ^c	not serious	none	214	398	-	MD 0.85 lower (1.65 lower to 0.05 lower)	⊕○○○ Very Low
Postnatal Head Circumference (cm) (6-9 yrs)										
FASD										
3	serious ^a	serious ^b	not serious	serious ^{d,f}	none	69	170	-	MD 0.59 lower (1.59 lower to 0.41 higher)	⊕○○○ Very Low
FAS										
7	serious ^a	not serious	serious ^c	not serious	none	383	956	-	MD 2.72 lower (2.94 lower to 2.50 lower)	⊕⊕○○ Low
pFAS (pFAS or pFAS/FAS or dysmorphic)										
6	serious ^a	serious ^b	serious ^c	not serious	none	195	775	-	MD 1.86 lower (2.40 lower to 1.31 lower)	⊕○○○ Very Low
Other (ARND, ND-AE, SE-AE, Non-syndromal)										
3	serious ^a	serious ^b	serious ^c	serious ^d	none	197	383	-	MD 0.81 lower (1.66 lower to 0.04 higher)	⊕○○○ Very Low
Postnatal Head Circumference (cms) (9-18 yrs)										
FASD										
1	serious ^a	not serious	serious ^c	serious ^{e,f}	none	13	12	-	MD 2.00 lower (3.70 lower to 0.30 lower)	⊕○○○ Very Low
FAS										
2	serious ^a	not serious	not serious	serious ^f	none	44	116	-	MD 3.44 lower (4.22 lower to 2.67 lower)	⊕⊕○○ Low
pFAS (pFAS or pFAS/FAS or dysmorphic)										
2	serious ^a	not serious	not serious	serious ^f	none	72	122	-	MD 1.33 lower (1.97 lower to 0.68 lower)	⊕⊕○○ Low
Other (ARND, ND-AE, SE-AE, Non-syndromal)										
4	serious ^a	serious ^b	serious ^c	serious ^d	none	264	204	-	MD 0.49 lower (1.08 lower to 0.10 higher)	⊕○○○ Very Low
Postnatal Head Circumference Centiles										
FASD – no studies										

FAS										
7	serious ^a	serious ^b	not serious	not serious	none	200	2475	-	MD 48.17 lower (58.24 lower to 38.11 lower)	⊕⊕○○ Low
pFAS (pFAS or pFAS/FAS or dysmorphic)										
9	serious ^a	serious ^b	not serious	not serious	none	264	2583	-	MD 25.12 lower (32.44 lower to 17.79 lower)	⊕⊕○○ Low
Other (ARND, ND-AE, SE-AE, Non-syndromal)										
7	serious ^a	serious ^b	not serious	serious ^d	none	209	2124	-	MD 11.32 lower (23.93 lower to 1.3 higher)	⊕○○○ Very Low
Postnatal Head Circumference <3 rd Percentile										
FASD										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	26	27	OR 0.69 (0.23 to 2.06)	-	⊕○○○ Very Low
FAS										
4	serious ^a	serious ^b	not serious	serious ^{e,f}	none	119	1525	OR 43.15 (14.11 to 131.97)	-	⊕○○○ Very Low
pFAS (pFAS or pFAS/FAS or dysmorphic)										
5	serious ^a	serious ^b	not serious	very serious ^{d,e,f}	none	162	1541	OR 4.59 (1.16 to 18.13)	-	⊕○○○ Very Low
Other (ARND, ND-AE, SE-AE, Non-syndromal)										
5	serious ^a	not serious	not serious	serious ^{e,f}	none	149	1541	OR 9.01 (4.06 to 20.04)	-	⊕⊕○○ Low
Postnatal Head Circumference <10 th Percentile										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	62	126	OR 24.18 (3.01 to 194.55)	-	⊕⊕○○ Low
FAS										
6	serious ^a	serious ^b	not serious	serious ^{e,f}	none	239	1756	OR 63.26 (15.78 to 253.70)	-	⊕○○○ Very Low
pFAS (pFAS or pFAS/FAS or dysmorphic)										
4	serious ^a	serious ^b	not serious	serious ^{e,f}	none	142	1525	OR 3.65 (1.51 to 8.80)	-	⊕○○○ Very Low
Other (ARND, ND-AE, SE-AE, Non-syndromal)										
5	serious ^a	not serious	not serious	serious ^{e,f}	none	242	1710	OR 4.23 (2.41 to 7.43)	-	⊕⊕○○ Low

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ($I^2 > 50\%$ and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) Wide 95% CIs for overall estimate; f) optimal information size criteria not met; g) While PAE and control group n's were not provided, the overall study sample size included in the data analysis = 47,178; h) One study provided sample size of 298.

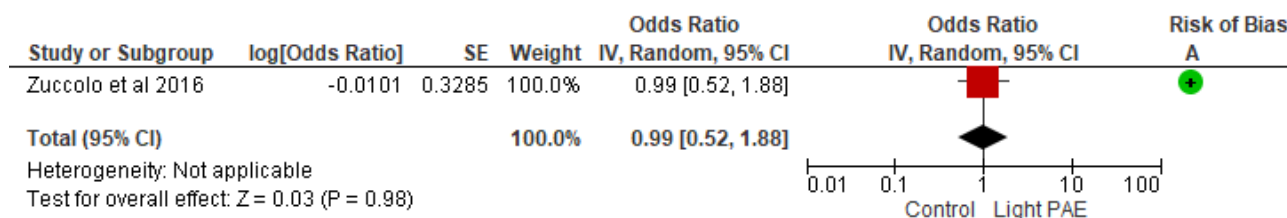
Meta-analyses for head circumference

EXPOSURE STUDIES

Birth head circumference outcomes

Head Circumference at Birth <10th Percentile

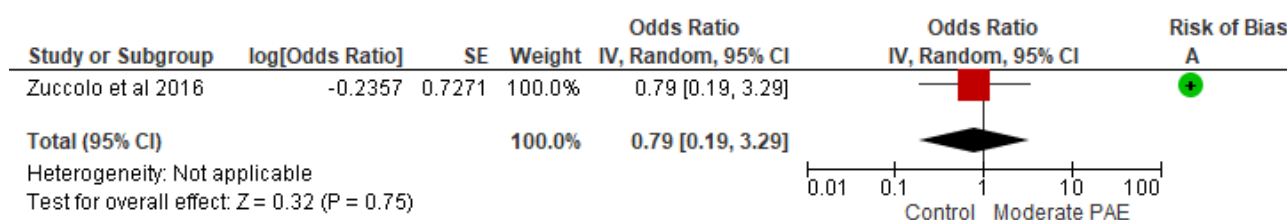
Light PAE and Head Circumference at Birth <10th Percentile (1 study)



Risk of bias legend

(A) Overall risk of Bias

Moderate PAE and Head Circumference at Birth <10th Percentile (1 study)



Risk of bias legend

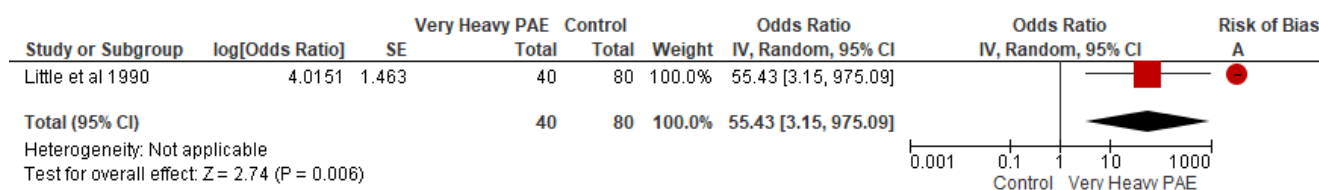
(A) Overall risk of Bias

Note: Zuccolo et al 2016 = group n's not provided

Heavy PAE and Head Circumference at Birth <10th Percentile (0 studies)

-

Very Heavy PAE and Head Circumference at Birth <10th Percentile (1 study)



Risk of bias legend

(A) Overall risk of Bias

Any Level PAE and Head Circumference at Birth <10th Percentile (0 studies)

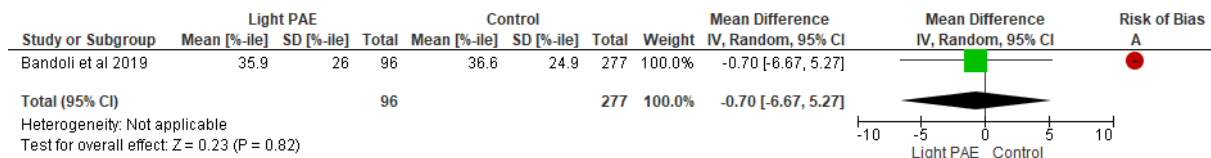
-

Confirmed PAE-Level Unquantifiable and Head Circumference at Birth (0 studies)

-

Head Circumference Percentile at Birth

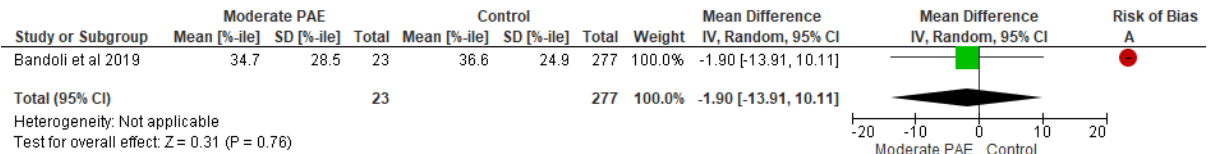
Light PAE and Head Circumference Percentile at Birth (1 study)



[Risk of bias legend](#)

(A) Overall risk of Bias

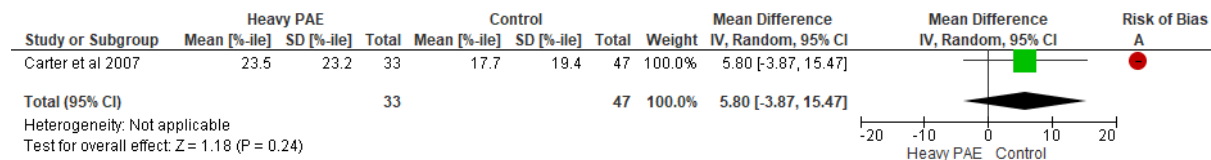
Moderate PAE and Head Circumference Percentile at Birth (1 study)



[Risk of bias legend](#)

(A) Overall risk of Bias

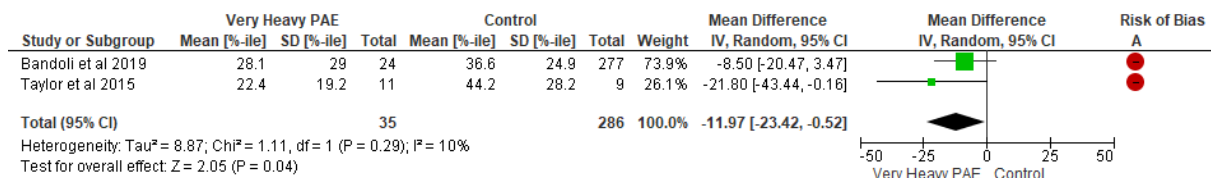
Heavy PAE and Head Circumference Percentile at Birth (1 study)



[Risk of bias legend](#)

(A) Overall risk of Bias

Very Heavy PAE and Head Circumference Percentile at Birth (2 studies)



[Risk of bias legend](#)

(A) Overall risk of Bias

Any Level PAE and Head Circumference Percentile at Birth (0 studies)

-

Confirmed PAE-Level Unquantifiable and Head Circumference Percentile at Birth (0 studies)

Head Circumference at Birth <3rd Percentile

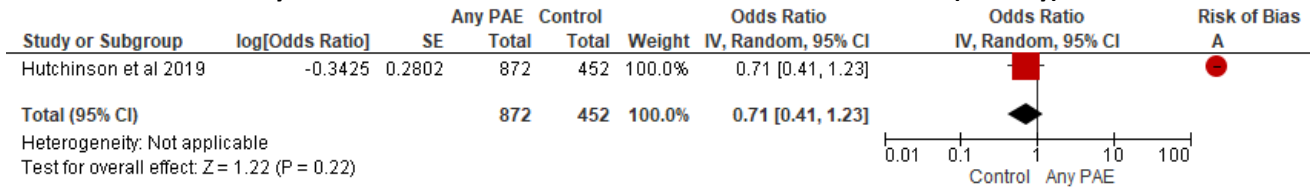
Light PAE and Head Circumference Percentile at Birth (0 studies)

Moderate PAE and Head Circumference Percentile at Birth (0 studies)

Heavy PAE and Head Circumference Percentile at Birth (0 studies)

Very Heavy PAE and Head Circumference Percentile at Birth (0 studies)

Any Level PAE and Head Circumference Percentile at Birth (1 study)



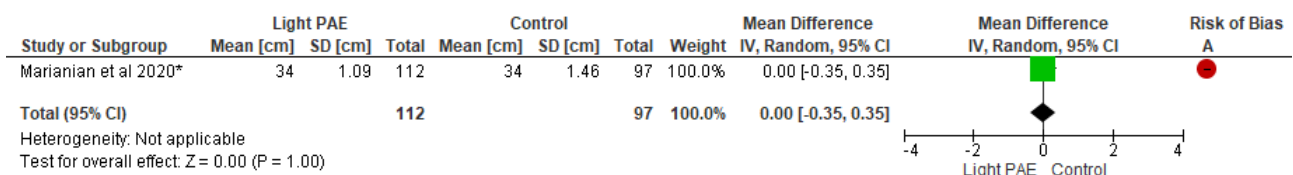
[Risk of bias legend](#)

(A) Overall risk of Bias

Confirmed PAE-Level Unquantifiable and Head Circumference Percentile at Birth (0 studies)

Head Circumference at Birth (Mean and SD)

Light PAE and Head Circumference at Birth (1 study)

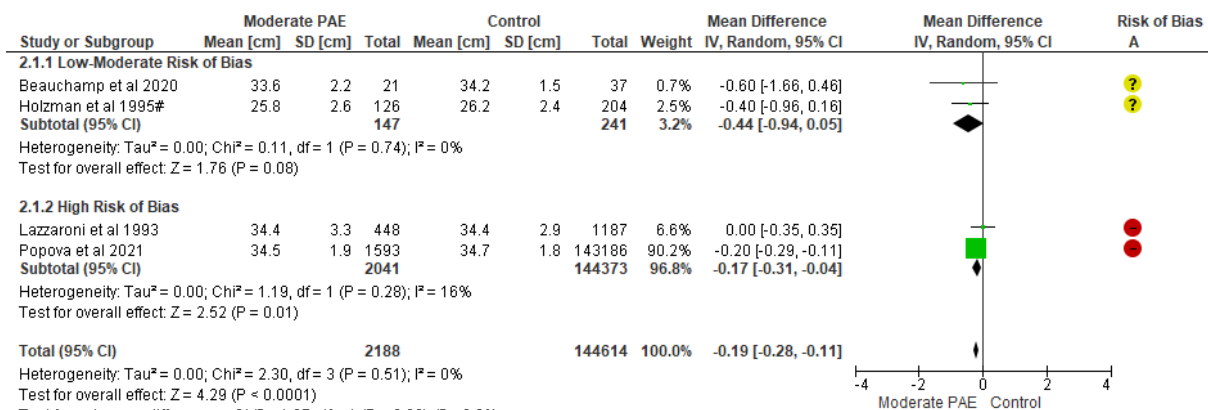


[Risk of bias legend](#)

(A) Overall risk of Bias

Note: Marianian et al 2020 = mean and SD estimated from median and interquartile range.

Moderate PAE and Head Circumference at Birth (4 studies)

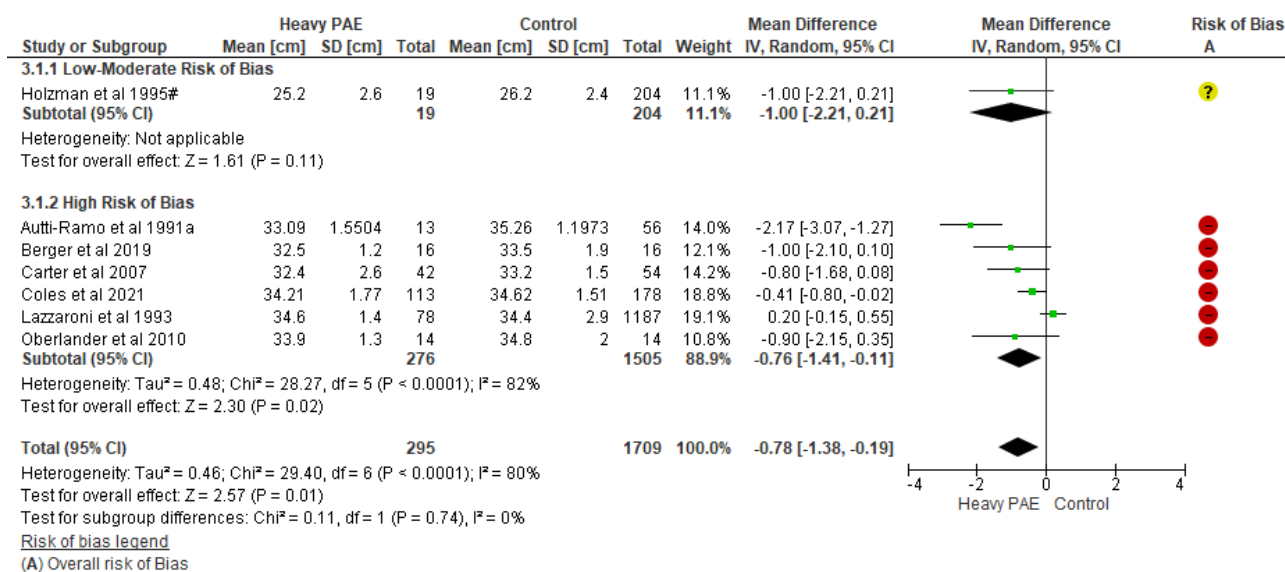


[Risk of bias legend](#)

(A) Overall risk of Bias

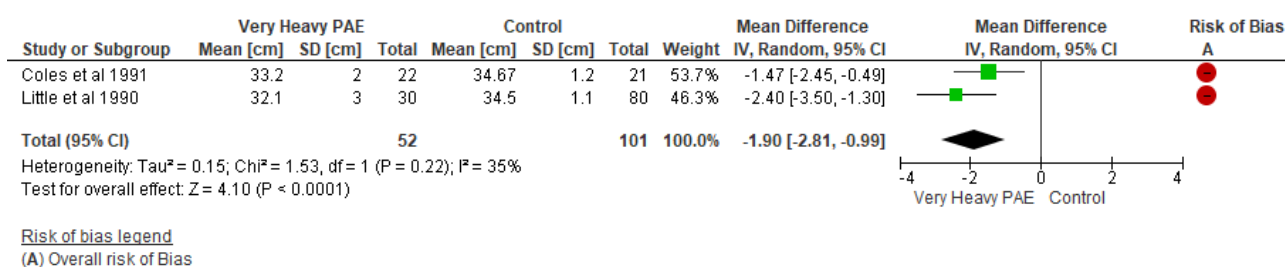
Note: #Holzman – sample were premature neonates

Heavy PAE and Head Circumference at Birth (7 studies)

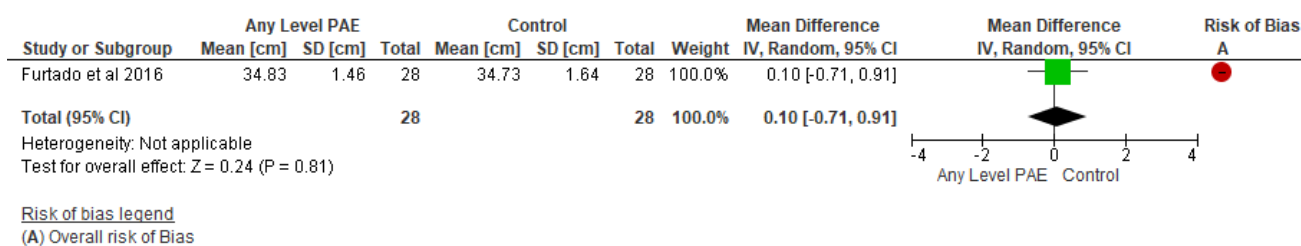


Note: #Holzman – sample were premature neonates.

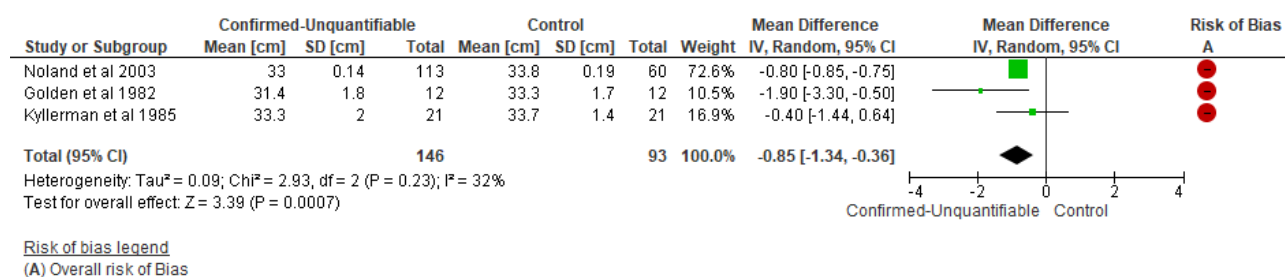
Very Heavy PAE and Head Circumference at Birth (2 studies)



Any Level PAE and Head Circumference at Birth (1 study)



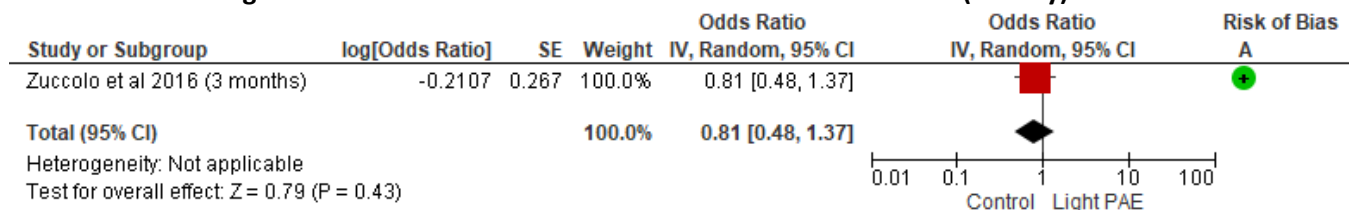
Confirmed PAE-Level Unquantifiable and Head Circumference at Birth (3 studies)



Postnatal head circumference

Postnatal Head Circumference <10th Percentile

Light PAE and Postnatal Head Circumference <10th Percentile (1 study)

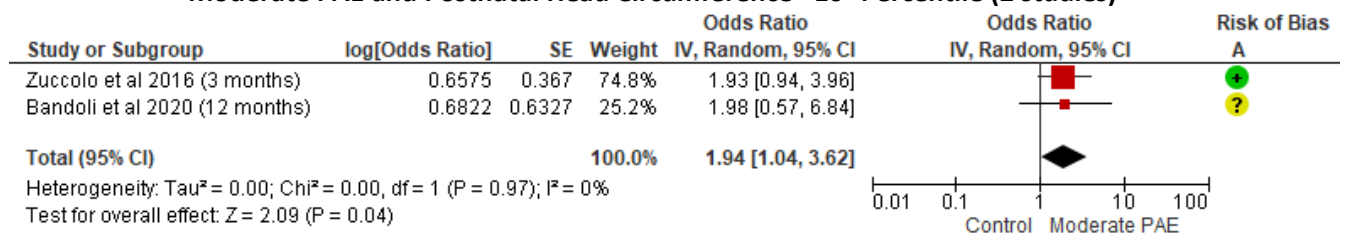


Risk of bias legend

(A) Overall risk of Bias

Note: Zuccolo et al 2016 = group n's not provided

Moderate PAE and Postnatal Head Circumference <10th Percentile (2 studies)

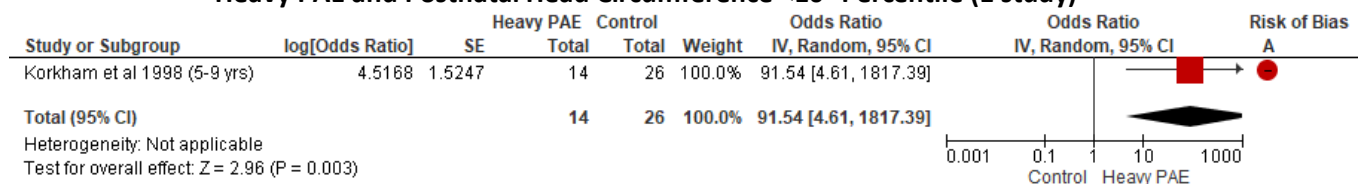


Risk of bias legend

(A) Overall risk of Bias

Note: Zuccolo et al 2016 = group n's not provided; Bandoli et al 2020, Moderate PAE, n = 45, No PAE control, n = 253.

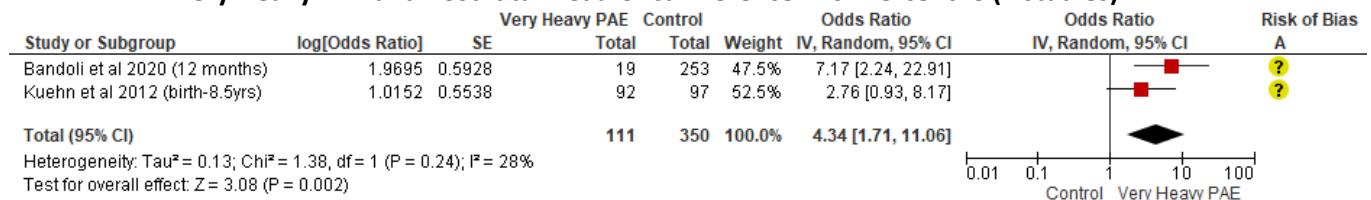
Heavy PAE and Postnatal Head Circumference <10th Percentile (1 study)



Risk of bias legend

(A) Overall risk of Bias

Very Heavy PAE and Postnatal Head Circumference <10th Percentile (2 studies)

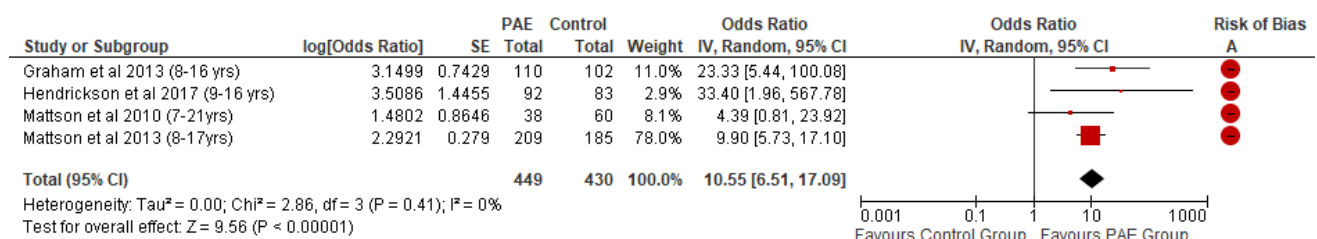


Risk of bias legend

(A) Overall risk of Bias

Any Level PAE and Postnatal Head Circumference <10th Percentile (0 studies)

Confirmed PAE-Level Unquantifiable and Postnatal Head Circumference <10th Percentile (4 studies)



Risk of bias legend

(A) Overall risk of Bias

Postnatal Head Circumference Percentile (Mean and SD)

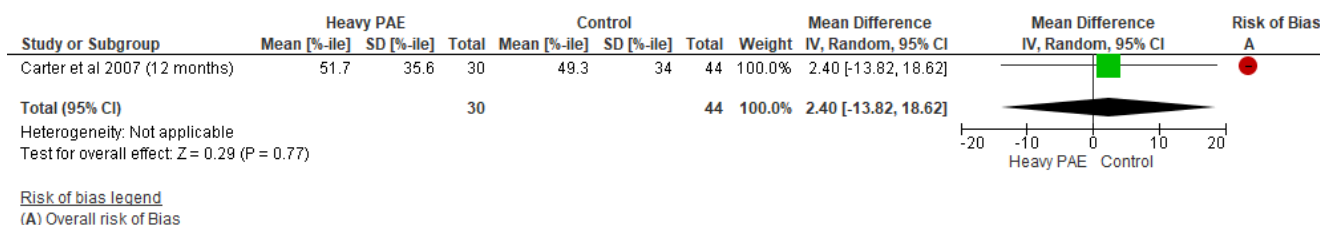
Light PAE and Postnatal Head Circumference Percentile (0 studies)

-

Moderate PAE and Postnatal Head Circumference Percentile (0 studies)

-

Heavy PAE and Postnatal Head Circumference Percentile (2 studies)



Very Heavy PAE and Postnatal Head Circumference Percentile (0 studies)

-

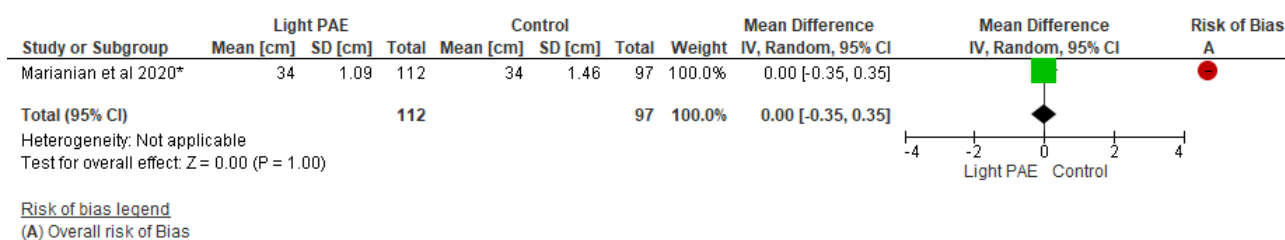
Any Level PAE and Postnatal Head Circumference Percentile (0 studies)

-

Confirmed PAE-Level Unquantifiable and Postnatal Head Circumference Percentile (0 studies)

Postnatal Head Circumference (Mean and SD)

Light PAE and Postnatal Head Circumference (1 study)

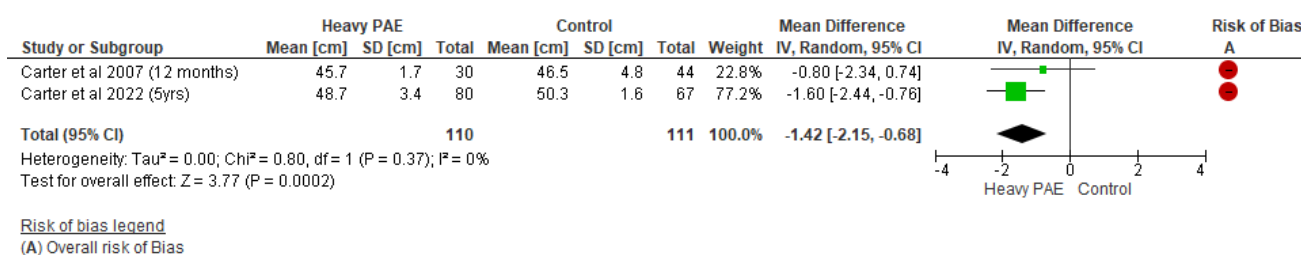


Note. Marianian et al 2020 = mean and SD estimated from median and interquartile range.

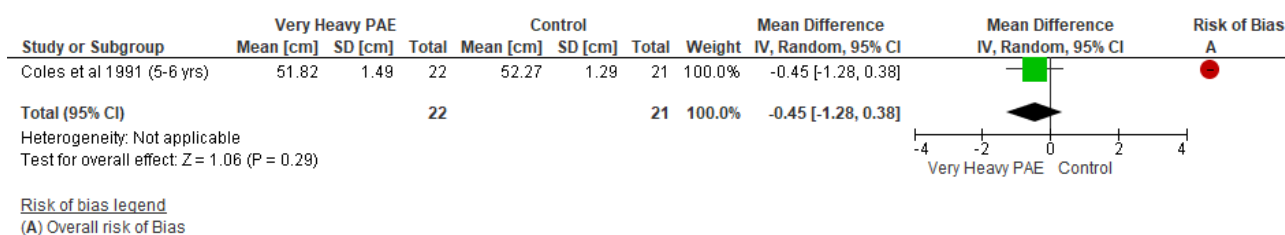
Moderate PAE and Postnatal Head Circumference (0 studies)

-

Heavy PAE and Postnatal Head Circumference (2 studies)



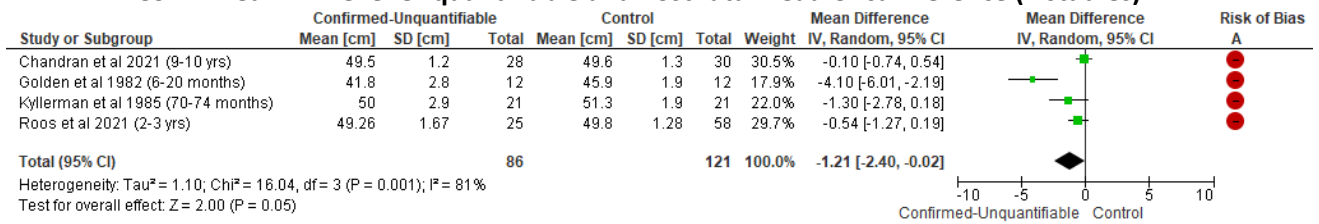
Very Heavy PAE and Postnatal Head Circumference (1 study)



Any Level PAE and Postnatal Head Circumference (0 studies)

-

Confirmed PAE-Level Unquantifiable and Postnatal Head Circumference (4 studies)



Risk of bias legend

(A) Overall risk of Bias

DIAGNOSED STUDIES

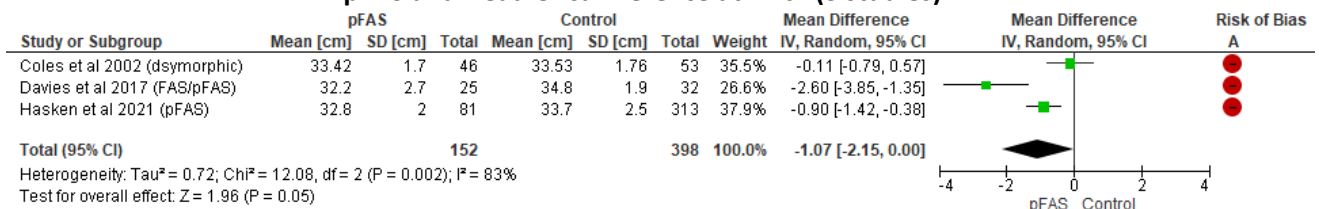
Birth head circumference outcomes

Head Circumference at Birth (Mean and SD)

FASD and Head Circumference at Birth (0 studies)

FAS and Head Circumference at Birth (0 studies)

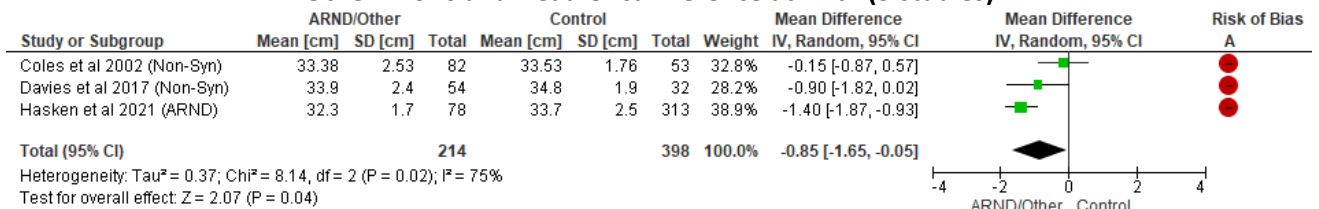
pFAS and Head Circumference at Birth (3 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

Other FASDs and Head Circumference at Birth (3 studies)



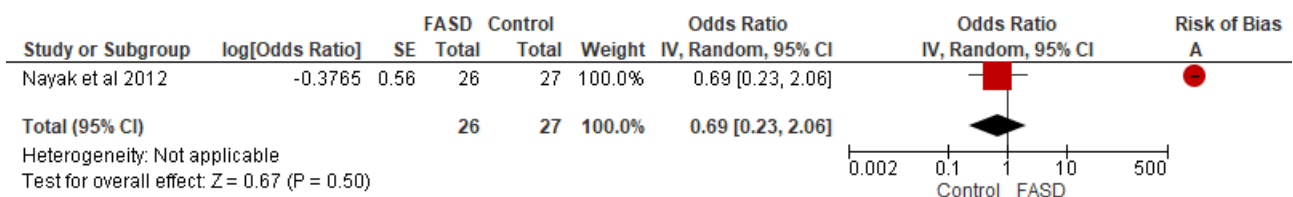
Risk of bias legend

(A) Overall Risk of Bias Score

Postnatal head circumference

Postnatal Head Circumference <3rd Percentile

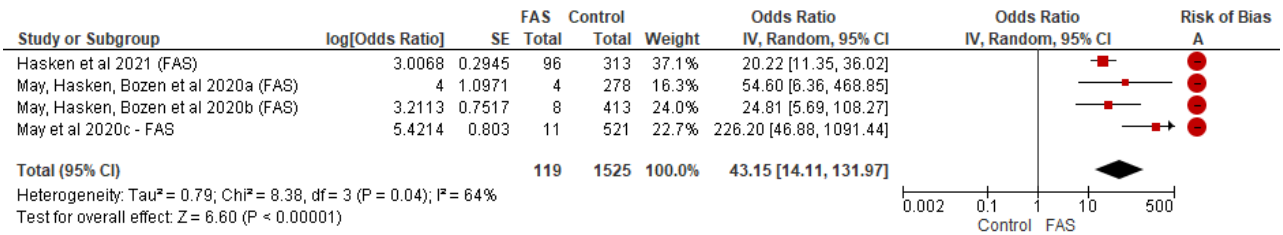
FASD and Postnatal Head Circumference <3rd Percentile (1 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

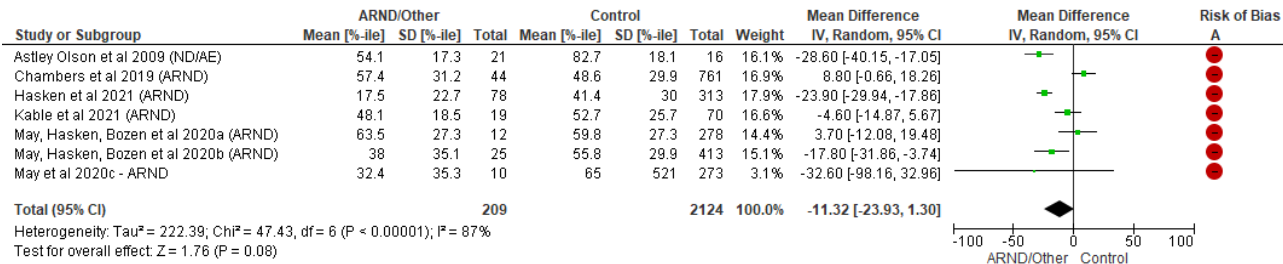
FAS and Postnatal Head Circumference <3rd Percentile (4 studies)



[Risk of bias legend](#)

(A) Overall Risk of Bias Score

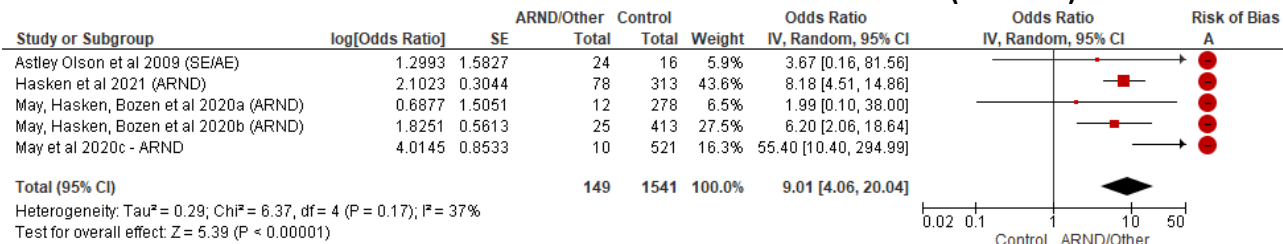
pFAS and Postnatal Head Circumference <3rd Percentile (5 studies)



[Risk of bias legend](#)

(A) Overall Risk of Bias Score

Other FASDs and Postnatal Head Circumference 3rd Percentile (5 studies)

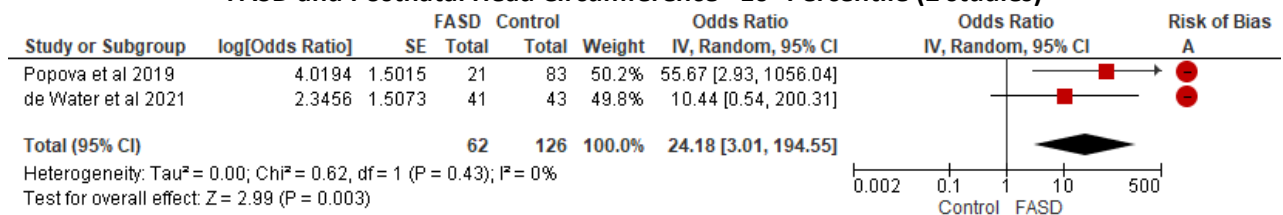


[Risk of bias legend](#)

(A) Overall Risk of Bias Score

Postnatal Head Circumference <10th Percentile

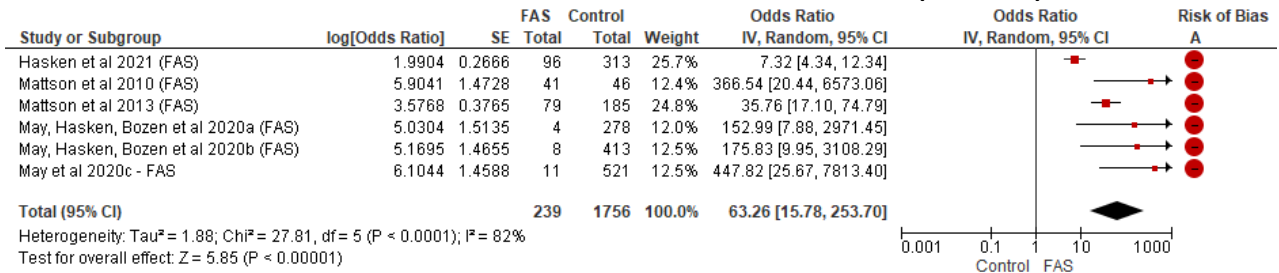
FASD and Postnatal Head Circumference <10th Percentile (2 studies)



[Risk of bias legend](#)

(A) Overall Risk of Bias Score

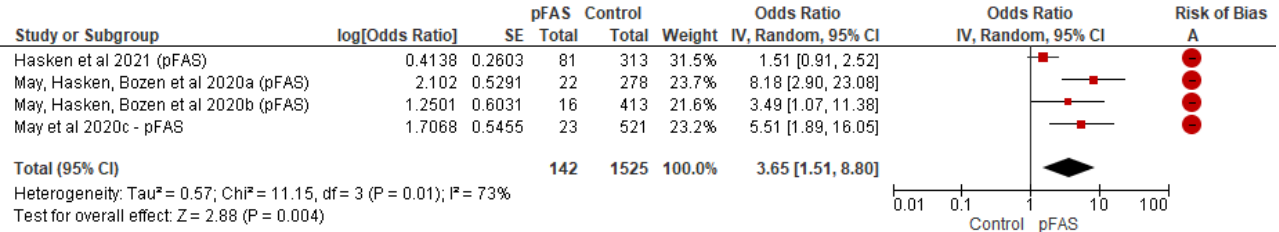
FAS and Postnatal Head Circumference <10th Percentile (6 studies)



[Risk of bias legend](#)

(A) Overall Risk of Bias Score

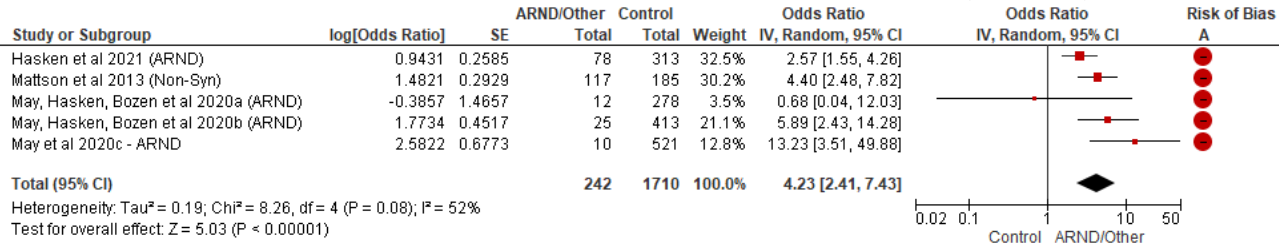
pFAS and Postnatal Head Circumference <10th Percentile (4 studies)



[Risk of bias legend](#)

(A) Overall Risk of Bias Score

Other FASDs and Postnatal Head Circumference <10th Percentile (5 studies)



[Risk of bias legend](#)

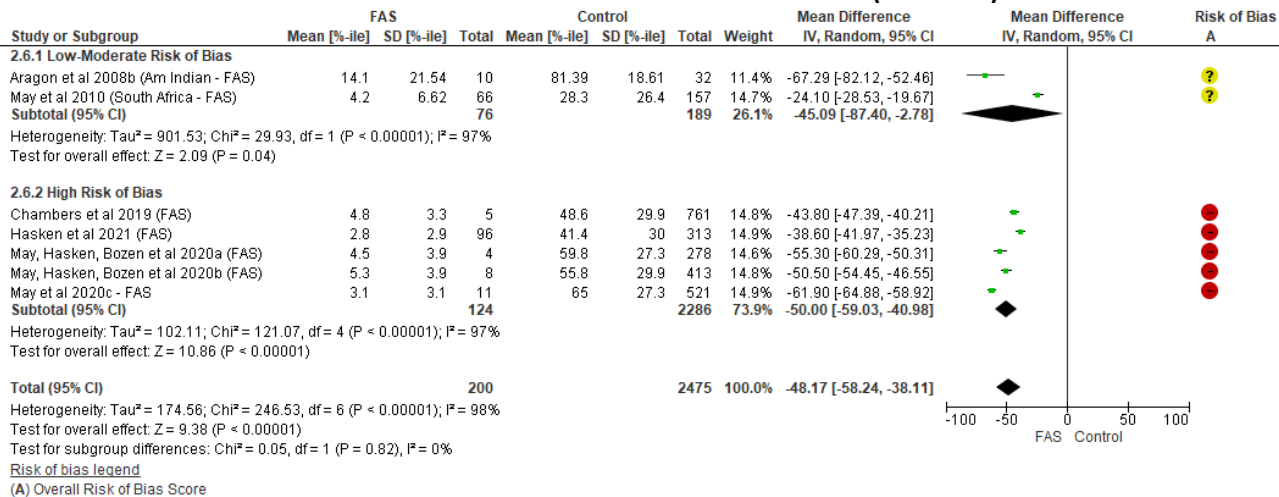
(A) Overall Risk of Bias Score

Postnatal Head Circumference Percentile

FASD and Postnatal Head Circumference Percentile (0 studies)

-

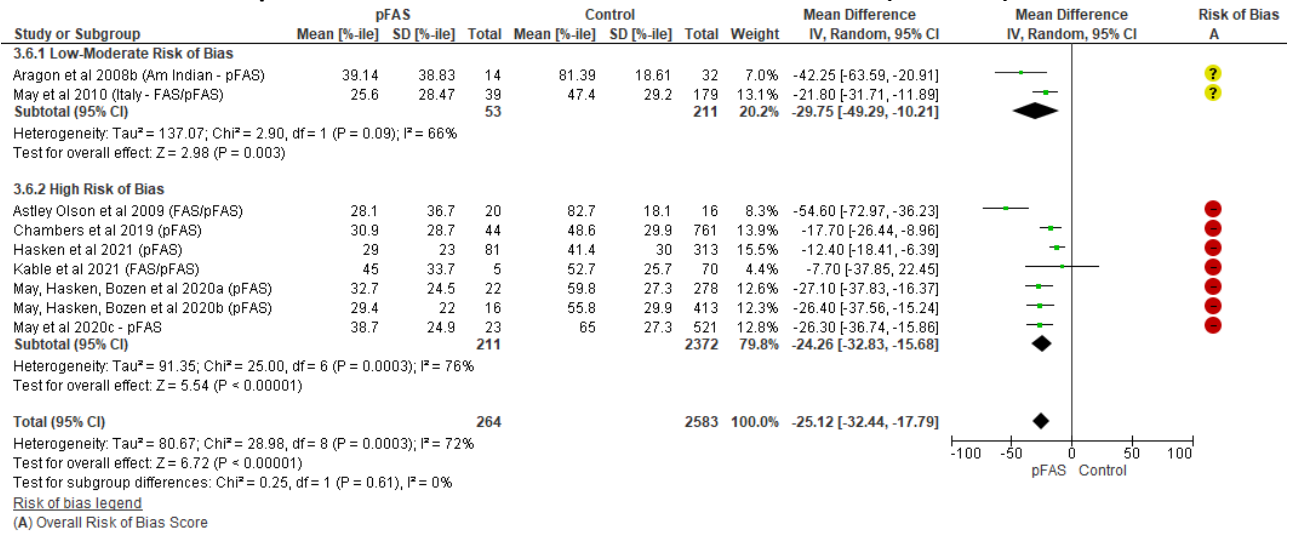
FAS and Postnatal Head Circumference Percentile (7 studies)



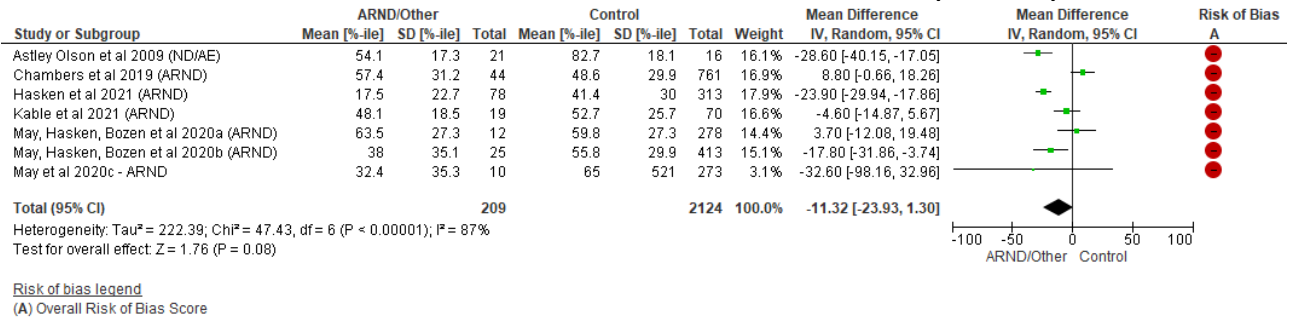
[Risk of bias legend](#)

(A) Overall Risk of Bias Score

pFAS and Postnatal Head Circumference Percentile (9 studies)

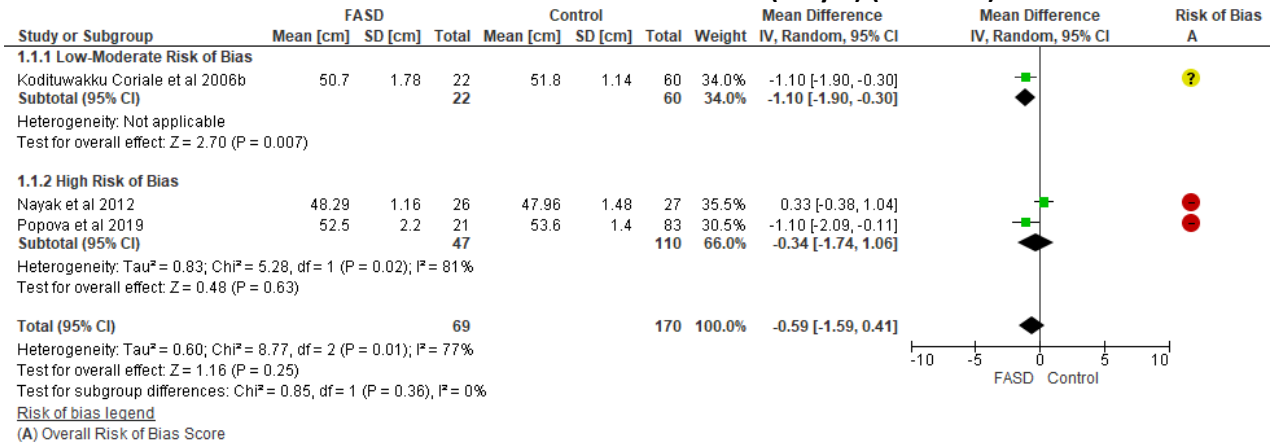


Other FASDs and Postnatal Head Circumference Percentile (7 studies)

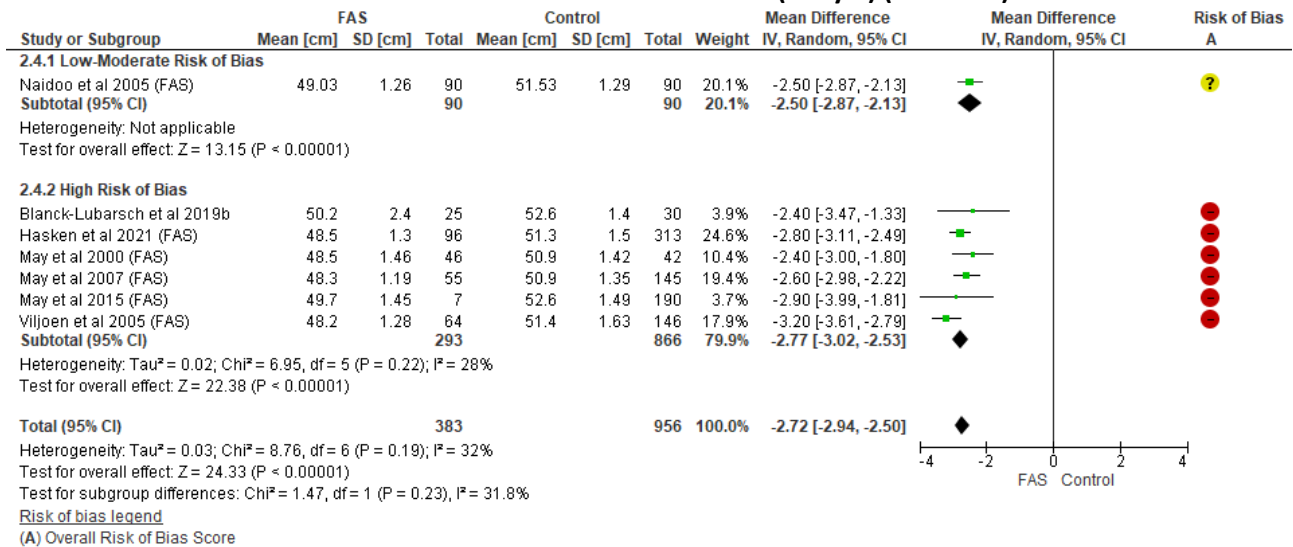


Postnatal Head Circumference (6-9 years)

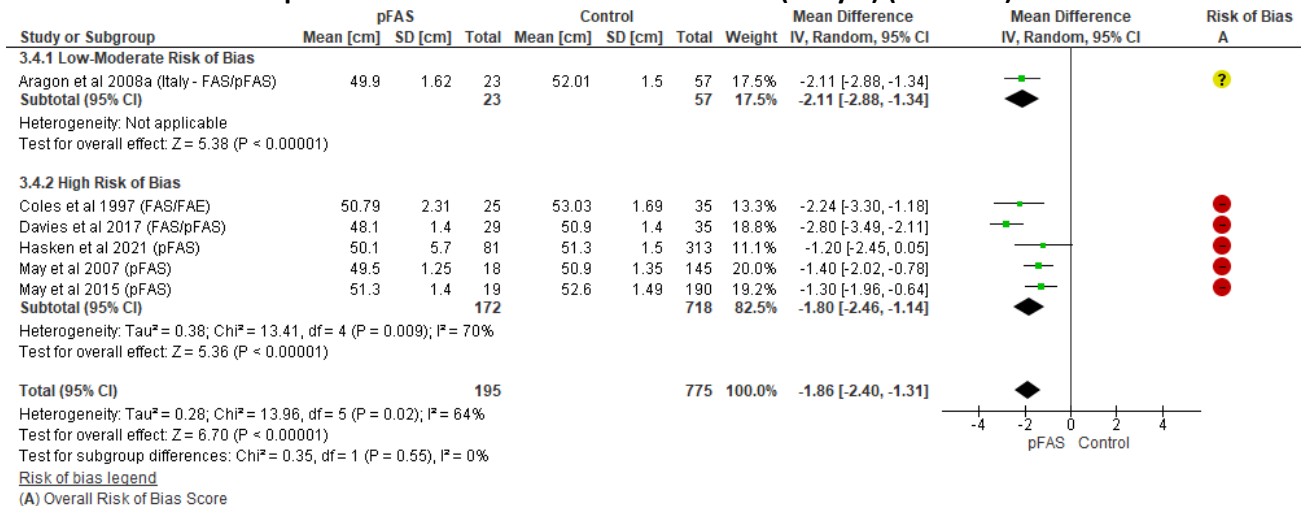
FASD and Postnatal Head Circumference (6-9yrs) (3 studies)



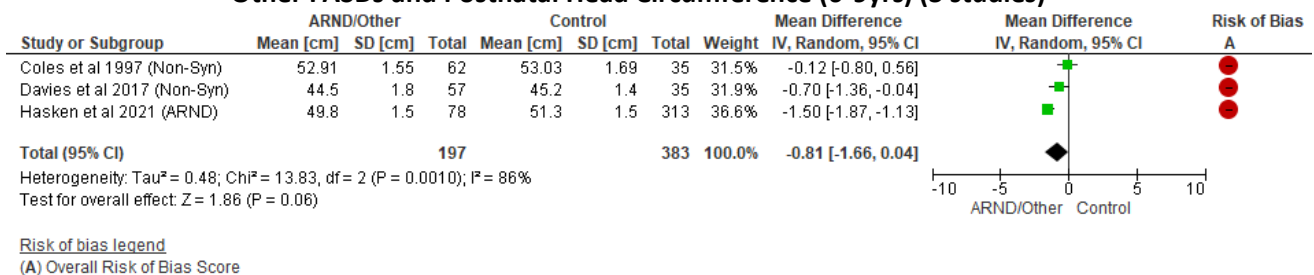
FAS and Postnatal Head Circumference (6-9 yrs) (7 studies)



pFAS and Postnatal Head Circumference (6-9 yrs) (6 studies)

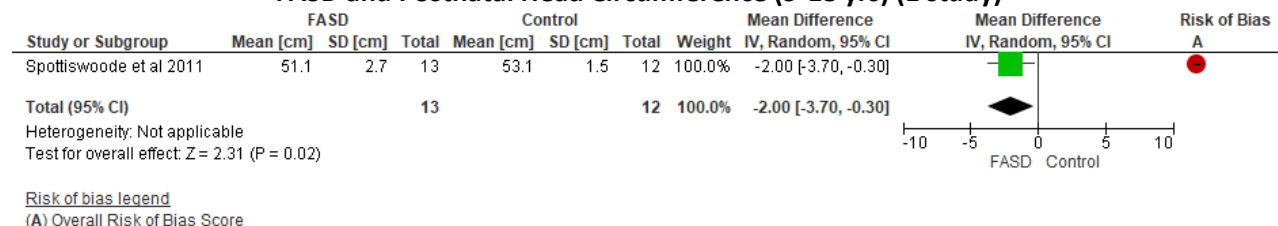


Other FASDs and Postnatal Head Circumference (6-9yrs) (3 studies)

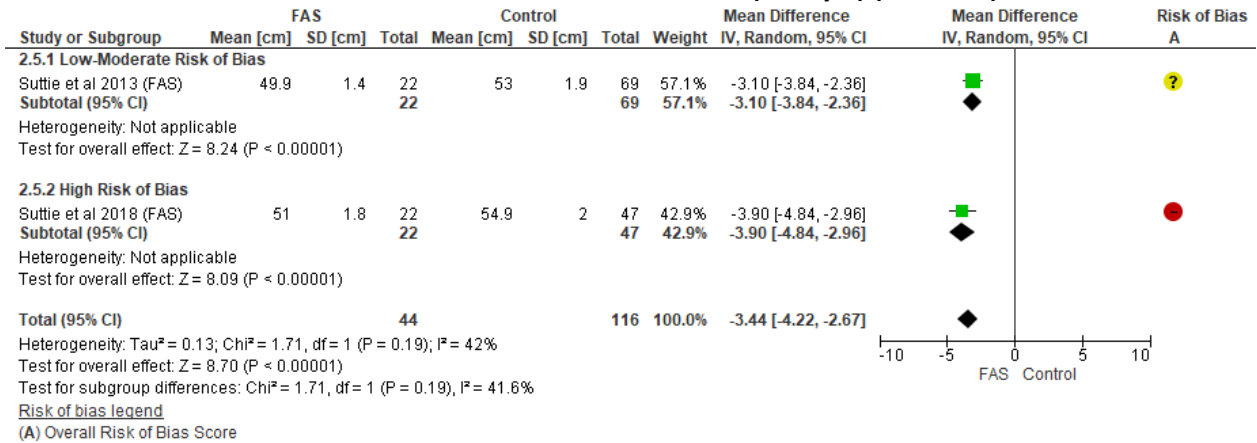


Postnatal Head Circumference (9-18 years)

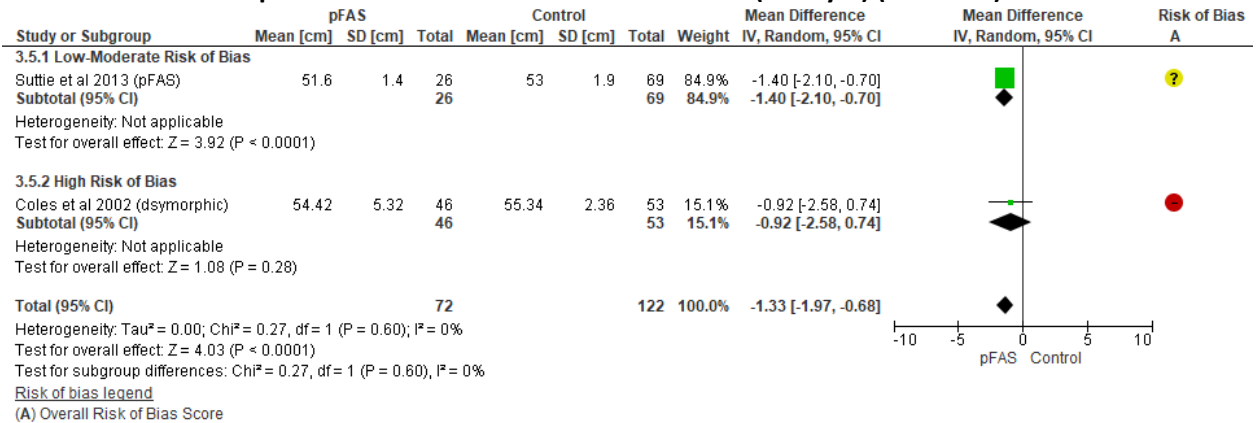
FASD and Postnatal Head Circumference (9-18 yrs) (1 study)



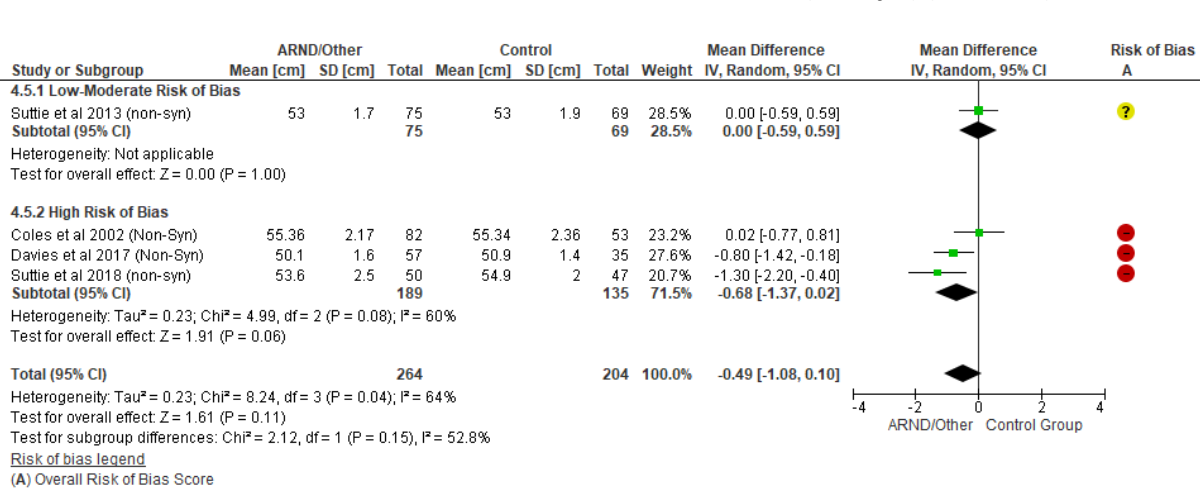
FAS and Postnatal Head Circumference (9-18 yrs) (2 studies)



pFAS and Postnatal Head Circumference (9-18 yrs) (2 studies)



Other FASDs and Postnatal Head Circumference (9-18 yrs) (4 studies)



Summary of available outcomes for structural brain abnormalities – Clinical MRI

Qualitative Clinical MRI		
Study type	Outcome	# studies
Exposure Studies	Frequency of clinically significant incidental findings	1 study: confirmed unquantified
Diagnosed Studies	Frequency of clinically significant incidental findings	2 studies: FAS/pFAS (dysmorphic) and ARND/Others (non-dysmorphic)
	Frequency of agenesis/hypogenesis of corpus callosum	2 studies: FAS/pFAS

Note. Triet et al 2020 had both exposure analyses and diagnosed analyses. Both were used in the meta-analysis.

GRADE ratings for structural brain abnormalities – Clinical MRI

	Certainty assessment					№ of patients		Effect		Certainty
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Frequency of clinically significant incidental findings										
Confirmed unquantified										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	164	163	OR 2.53 (0.48 to 13.24)	-	⊕○○○ Very Low
DIAGNOSED STUDIES										
Frequency of clinically significant incidental findings										
FAS/pFAS (dysmorphic groups)										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	6/57	2/179	OR 6.97 (1.46 to 33.34)	-	⊕⊕○○ Low
ARND/Others (non-dysmorphic groups)										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	3/118	2/179	OR 1.36 (0.09 to 20.24)	-	⊕○○○ Very Low
Frequency of agenesis/hypogenesis of the corpus callosum										
FAS/pFAS										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	4/33	0/28	OR 4.92 (0.54 to 44.79)	-	⊕○○○ Very Low

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

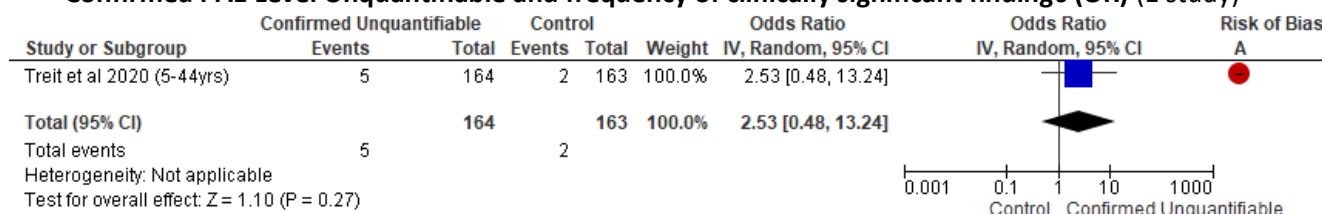
Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ($I^2 > 50\%$ and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) Wide 95% CIs for overall estimate; f) optimal information size criteria not met; g) While PAE and control group n's were not provided, the overall study sample size included in the data analysis = 47,178; h) One study provided sample size of 298.

Meta-analyses for clinical MRI

Exposure Studies

Frequency of clinically significant incidental findings (OR)

Confirmed PAE Level Unquantifiable and frequency of clinically significant findings (OR) (1 study)



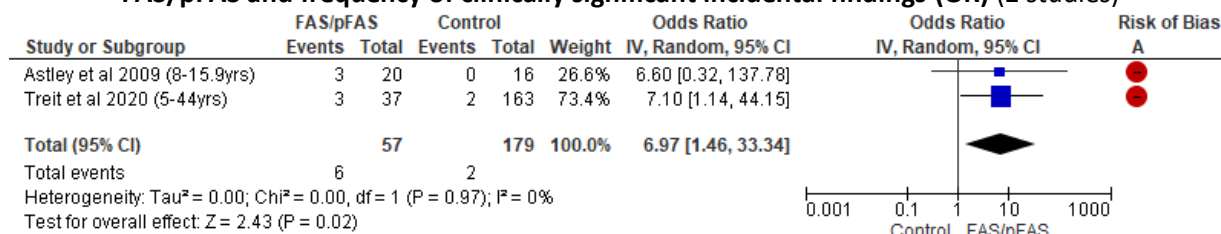
Risk of bias legend

(A) Overall RoB

Diagnosed Studies

Frequency of clinically significant incidental findings (OR)

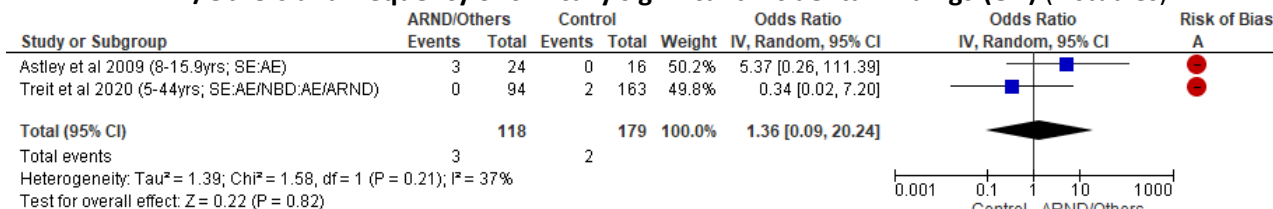
FAS/pFAS and frequency of clinically significant incidental findings (OR) (2 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and frequency of clinically significant incidental findings (OR) (2 studies)

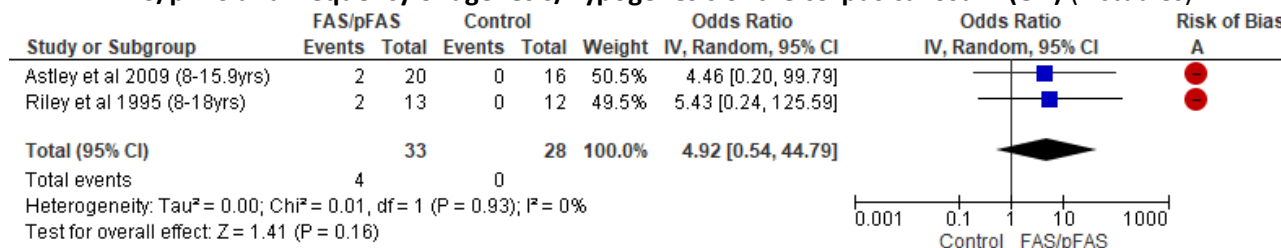


Risk of bias legend

(A) Overall RoB

Frequency of agenesis/hypogenesis of the corpus callosum (OR)

FAS/pFAS and frequency of agenesis/hypogenesis of the corpus callosum (OR) (2 studies)



Risk of bias legend

(A) Overall RoB

Note: Riley et al 1985 included 11 participants with FAS and 2 with PAE.

Summary of available outcomes for structural brain abnormalities – Advanced quantitative research MRI

Advanced quantitative research MRI		
Study type	Outcome	# studies
Exposure studies	Total Intracranial volume, total brain volume (cm ³)	8 PAE studies: 1x light PAE, 1x moderate PAE, 2x very heavy PAE, 3x confirmed unquantifiable
	Left hippocampus (mm ³)	2x PAE studies: 2x confirmed unquantifiable
	Right Hippocampus (mm ³)	1x PAE studies: 1x confirmed unquantifiable
	Grey matter volume (cm ³)	2x PAE studies: 1x very heavy PAE, 1x confirmed unquantifiable
	Right putamen volume (mm/cm ³)	2x PAE studies: 2x confirmed unquantifiable
	Left putamen volume (mm/cm ³)	2x PAE studies: 2x confirmed unquantifiable
	Left amygdala (mm ³)	2x PAE studies: 2x confirmed unquantifiable
	Right amygdala (mm ³)	2x PAE studies: 2x confirmed unquantifiable
	Left thalamus (mm ³)	2x PAE studies: 2x confirmed unquantifiable
	Right thalamus (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Left Caudate (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Right Caudate (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Left Pallidum (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Right Pallidum (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Left Nucleus Accumbens (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Right Nucleus Accumbens (mm ³)	1x PAE study: 1x confirmed unquantifiable
	White matter volume (cm ³)	2x PAE studies: 2x very heavy PAE
	Total cortical brain volume (cm ³)	2x PAE studies: 1x light PAE, 1x confirmed unquantifiable
	Left Caudate (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Right Caudate (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Left Hemisphere Volume (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Right Hemisphere Volume (mm ³)	1x PAE study: 1x confirmed unquantifiable
	Grey/white matter ratio	1x PAE study: 1x very heavy PAE
	White matter fraction	1x PAE study: 1x very heavy PAE
	Cranial white matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Cranial grey matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Left inferior parietal gyrus (cm ³)	1x PAE study: 1x confirmed unquantifiable
	Left middle frontal (caudal) gyrus (cm ³)	1x PAE study: 1x confirmed unquantifiable
	Left paracentral gyrus (cm ³)	1x PAE study: 1x confirmed unquantifiable
	Left precentral gyrus (cm ³)	1x PAE study: 1x confirmed unquantifiable
	Left precuneus (cm ³)	1x PAE study: 1x confirmed unquantifiable
	Right precuneus (cm ³)	1x PAE study: 1x confirmed unquantifiable
	Right inferior parietal (mm)	1x PAE study: 1x confirmed unquantifiable
	Left postcentral gyrus (mm)	1x PAE study: 1x confirmed unquantifiable
	Right postcentral gyrus (mm)	1x PAE study: 1x confirmed unquantifiable
	Cingulate grey matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Cingulate white matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Left cingulate grey matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Right cingulate grey matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Anterior subdivision cingulate grey matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Posterior subdivision cingulate grey matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Left cingulate white matter (cc)	1x PAE study: 1x confirmed unquantifiable
	Right cingulate white matter (cc)	1x PAE study: 1x confirmed unquantifiable

Anterior subdivision cingulate white matter (cc)	1x PAE study: 1x confirmed unquantifiable
Posterior subdivision cingulate white matter (cc)	1x PAE study: 1x confirmed unquantifiable
Anterior vermis (I-V) area (mm ³)	1x PAE study: 1x confirmed unquantifiable
Superior posterior vermis (VI-VII) area (mm ³)	1x PAE study: 1x confirmed unquantifiable
Inferior posterior vermis (VIII-X) area (mm ³)	1x PAE study: 1x confirmed unquantifiable
Corpus callosum and corona radiata (CCCR) (FA)	1x PAE study: 1x very heavy PAE
Left hemispheric projection fibres (L-PROJ) (FA)	1x PAE study: 1x very heavy PAE
Right hemispheric projection fibres (R-PROJ) (FA)	1x PAE study: 1x very heavy PAE
Left hemispheric association fibres (L-ASSOC) (FA)	1x PAE study: 1x very heavy PAE
Right hemispheric association fibres (R-ASSOC) (FA)	1x PAE study: 1x very heavy PAE
Left paracentral lobule (FA)	1x PAE study: 1x light PAE
Left middle cingulate area (FA)	1x PAE study: 1x light PAE
Left middle frontal area (FA)	1x PAE study: 1x light PAE
Left superior frontal area (FA)	1x PAE study: 1x light PAE
Left middle occipital area (FA)	1x PAE study: 1x light PAE
Left angular area (FA)	1x PAE study: 1x light PAE
Left supramarginal area (FA)	1x PAE study: 1x light PAE
Left postcentral gyrus area (FA)	1x PAE study: 1x light PAE
Left precentral area (FA)	1x PAE study: 1x light PAE
Left planum temporale (FA)	1x PAE study: 1x light PAE
Left anterior lateral sulcus area (FA)	1x PAE study: 1x light PAE
Left central sulcus area (FA)	1x PAE study: 1x light PAE
Left inferior occipital area (FA)	1x PAE study: 1x light PAE
Left inferior parietal area (FA)	1x PAE study: 1x light PAE
Left superior occipital area (FA)	1x PAE study: 1x light PAE
Left postcentral area (FA)	1x PAE study: 1x light PAE
Left superior precentral area (FA)	1x PAE study: 1x light PAE
Right superior parietal lobule (FA)	1x PAE study: 1x light PAE
Right middle occipital area (FA)	1x PAE study: 1x light PAE
Left putamen (grey matter) (FA)	1x PAE study: 1x light PAE
Right pregenual ACC	1x PAE study: 1x confirmed unquantifiable
Right anterior MCC	1x PAE study: 1x confirmed unquantifiable
Right rostral cingulate cortex	1x PAE study: 1x confirmed unquantifiable
Left pregenual ACC	1x PAE study: 1x confirmed unquantifiable
Left anterior MCC	1x PAE study: 1x confirmed unquantifiable
Left rostral cingulate cortex	1x PAE study: 1x confirmed unquantifiable
Right rostral ACC	1x PAE study: 1x confirmed unquantifiable
Left rostral ACC	1x PAE study: 1x confirmed unquantifiable
Right caudal ACC	1x PAE study: 1x confirmed unquantifiable
Left caudal ACC	1x PAE study: 1x confirmed unquantifiable
Total brain volume/intracranial volume (cm ³)	10x studies: 6x FASD, 4x FAS/pFAS, 2x ARND/Others
Right hippocampal volume (mm ³)	6x studies: 3x FASD, 3x FAS/pFAS, 3x ARND/Others
Left hippocampal volume (mm ³)	6x studies: 4x FASD, 2x FAS/pFAS, 3x ARND/Others

Diagnosed studies	Total hippocampal volume (cm ³)	5x studies: 2x FASD, 1x FAS/pFAS, 3x ARND/Others
	Right caudate volume (mm ³)	5x studies: 1x FASD, 4x FAS/pFAS, 2x ARND/Others
	Left caudate volume (mm ³)	5x studies: 1x FASD, 4x FAS/pFAS, 2x ARND/Others
	Total caudate volume (cm ³)	3x studies: 1x FASD, 1x FAS
	Total putamen volume (cm ³)	3x studies: 2x FASD, 1x FAS/pFAS, 1x ARND/Others
	Right putamen volume (cm ³)	3x studies: 2x FASD, 1x FAS/pFAS, 1x ARND/Others
	Left putamen volume (cm ³)	3x studies: 2x FASD, 1x FAS/pFAS, 1x ARND/Others
	Corpus callosum volume (mm ³)	2x studies: 2x FAS/pFAS, 1x ARND/Others
	Total grey matter volume (cm ³)	4x studies: 3x FASD, 1x FAS/pFAS
	Cortical grey matter volume (cm ³)	2x studies: 2x FASD
	Total Subcortical grey matter (cm ³)	4x studies: 4x FASD
	Total white matter volume (cm ³)	4x studies: 3x FASD, 1x FAS, 1x ARND/Others
	Grey & white tissue volume (cm ³)	1x study: 1x FASD
	Frontal lobe volume (cm ³)	1x study: 1x FAS/pFAS, 1x ARND/Others
	Genu corpus callosum (FA)	4 studies: 3x FASD, 1x FAS, 1x ARND/Others
	Rostral body corpus callosum (FA)	3 studies: 2x FASD, 1x FAS, 1x ARND/Others
	Anterior midbody corpus callosum (FA)	3 studies: 2x FASD, 1x FAS, 1x ARND/Others
	Posterior midbody corpus callosum (FA)	3 studies: 2x FASD, 1x FAS, 1x ARND/Others
	Isthmus corpus callosum (FA)	4x studies: 2x FASD, 2x FAS/pFAS, 2x ARND/Others
	Splenium corpus callosum (FA)	5x studies: 3x FASD, 2x FAS/pFAS, 2x ARND/Others
	Fusiform gyrus (mm ³)	2x studies: 1x FASD, 1x ARND/Others
	Cerebellar grey matter (cm ³)	3 studies: 1x FASD, 2x FAS/pFAS, 2x ARND/Others
	Cerebellar white matter (cm ³)	3 studies: 1x FASD, 2x FAS/pFAS, 2x ARND/Others
	Cerebellar volume (cm ³)	2 studies: 1x FASD, 1x FAS, 1x ARND/Others
	Medial orbital frontal (mm ³)	2 studies: 1x FASD, 1x ARND/Others
	Total cranial volume (cm ³)	1x study: 1x FAS
	Hippocampus	1x study: 1x FASD
	Left amygdala (cm ³)	2 studies: 2x FASD
	Right amygdala (cm ³)	2 studies: 2x FASD
	Left thalamus (cm ³)	2 studies: 2x FASD
	Right thalamus (cm ³)	2 studies: 2x FASD
	Thalamus (cm ³)	2 studies: 2x FASD
	Amygdala (cm ³)	2 studies: 2x FASD
	Frontal lobe grey matter volume (cm ³)	1 study: 1x FAS/pFAS, 1x ARND/Others
	Frontal lobe white matter volume (cm ³)	1 study: 1x FAS/pFAS, 1x ARND/Others
	Right frontal lobe	1x study: 1x ARND/Others
	Left frontal lobe	1x study: 1x ARND/Others
	Frontal pole (mm ³)	1x study: 1x ARND/Others
	Lateral OFC (mm ³)	1x study: 1x FASD
	Right parietal lobe	1x study: 1x ARND/Others
	Left parietal lobe	1x study: 1x ARND/Others
	Right temporal lobe	1x study: 1x ARND/Others
	Left temporal lobe	1x study: 1x ARND/Others
	Temporal pole (mm ³)	1x study: 1x FASD
	Right occipital lobe	1x study: 1x ARND/Others
	Left occipital lobe	1x study: 1x ARND/Others
	Caudate and putamen volume (cm ³)	1x study: 1x FAS/pFAS, 1x ARND/Others

Left Globus Pallidus (cm ³)	1x study: 1x FASD
Globus Pallidus (cm ³)	1x study: 1x FASD
Right Globus Pallidus (cm ³)	1x study: 1x FASD
Right anterior hippocampal volume (mm ³)	1x study: 1x ARND/Others
Right posterior hippocampal volume (mm ³)	1x study: 1x ARND/Others
Left anterior hippocampal volume (mm ³)	1x study: 1x ARND/Others
Left posterior hippocampal volume (mm ³)	1x study: 1x ARND/Others
Parahippocampal gyrus (mm ³)	1x study: 1x ARND/Others
Entorhinal (mm ³)	1x study: 1x ARND/Others
Parasubiculum	1x study: 1x FASD
Presubiculum	1x study: 1x FASD
Subiculum	1x study: 1x FASD
CA1	1x study: 1x FASD
CA3	1x study: 1x FASD
CA4	1x study: 1x FASD
HATA	1x study: 1x FASD
Fimbria	1x study: 1x FASD
Fissure	1x study: 1x FASD
Tail	1x study: 1x FASD
Caudal middle frontal gyrus (mm ³)	1x study: 1x ARND/Others
Superior frontal (mm ³)	1x study: 1x ARND/Others
Rostral medial frontal (mm ³)	1x study: 1x ARND/Others
Pars opercularis (mm ³)	1x study: 1x ARND/Others
Pars triangularis (mm ³)	1x study: 1x ARND/Others
Pars orbitalis (mm ³)	1x study: 1x ARND/Others
Left nucleus accumbens (mm ³)	1x study: 1x FAS/pFAS, 1x ARND/Others
Right nucleus accumbens (mm ³)	1x study: 1x FAS/pFAS, 1x ARND/Others
PCC (mm ³)	1x study: 1x FASD
Precuneus (mm ³)	1x study: 1x FASD
STG (mm ³)	1x study: 1x FASD
CC – Splenium area (mm ³)	1x study: 1x ARND/Others
CC – Isthmus area (mm ³)	1x study: 1x ARND/Others
CC – Posterior midbody area (mm ³)	1x study: 1x ARND/Others
CC – Anterior midbody (mm ³)	1x study: 1x ARND/Others
CC – Genu area (mm ³)	1x study: 1x ARND/Others
Left middle cerebellar peduncle (FA)	1x study: 1x FASD
Superior longitudinal fasciculus (FA)	1x study: 1x FASD
Inferior fronto-occipital fasciculus (FA)	1x study: 1x FASD
Inferior longitudinal fasciculus (FA)	1x study: 1x FASD
Left inferior longitudinal fasciculus (FA)	1x study: 1x FAS/pFAS
Right inferior longitudinal fasciculus (FA)	1x study: 1x FAS/pFAS
Right anterior temporal lobe (FA)	1x study: 1x FASD
Right posterior temporal lobe (FA)	1x study: 1x FASD
Left anterior temporal lobe (FA)	1x study: 1x FASD
Left posterior temporal lobe (FA)	1x study: 1x FASD
Body corpus callosum (FA)	1x study: 1x FASD
Left splenium (FA)	1x study: 1x FASD
Right splenium (FA)	1x study: 1x FASD
Brainstem (FA)	1x study: 1x FASD
Uncinate fasciculus (FA)	1x study: 1x FASD
Cingulum (FA)	1x study: 1x FASD
Corticospinal tract (FA)	1x study: 1x FASD
Cortical grey matter	1x study: 1x FASD
Cortical grey matter Left	1x study: 1x FASD
Cortical grey matter Right	1x study: 1x FASD
Total cerebrum (cm ³)	1x study: 1x FASD

	Total cerebrum (grey matter and white matter) (cm ³)	1x study: 1x FASD
	Cerebrum white matter left	1x study: 1x FASD
	Cerebrum white matter right	1x study: 1x FASD
	Cerebrum white matter	1x study: 1x FASD
	Cerebellum grey matter	1x study: 1x FASD
	Cerebellum white matter	1x study: 1x FASD
	Cerebellum grey matter left	1x study: 1x FASD
	Cerebellum grey matter right	1x study: 1x FASD
	Cerebellum white matter left	1x study: 1x FASD
	Cerebellum white matter right	1x study: 1x FASD
	Caudate left	1x study: 1x FASD
	Caudate right	1x study: 1x FASD
	Pallidum	1x study: 1x FASD
	Pallidum left	1x study: 1x FASD
	Pallidum right	1x study: 1x FASD
	Bilateral cingulum bundle	1x study: 1x FAS/pFAS
	Bilateral Hippocampus Volume (cc)	1x study: 1x FASD
	Bilateral Caudate Nucleus Volume (cc)	1x study: 1x FASD
	Bilateral Frontal Lobe Volume (cc)	1x study: 1x FASD
	Bilateral Cerebellum Volume (cc)	1x study: 1x FASD
	Bilateral Parietal Lobe Volume (cc)	1x study: 1x FASD
	Bilateral Temporal Lobe Volume (cc)	1x study: 1x FASD
	Bilateral Occipital Lobe Volume (cc)	1x study: 1x FASD
	Bilateral Lenticular Nucleus Volume (cc)	1x study: 1x FASD

Note. Included is a summary of all outcomes identified. Only completed GRADE ratings and plots for outcomes with 2 or more studies – highlighted in grey.

GRADE ratings quantitative MRI studies

	Certainty assessment					№ of patients		Effect		Certainty
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Total Brain/Intracranial volume (cm³) (m/SD)										
Very heavy PAE										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	22	18	SMD 0.22 lower (1.03 lower to 0.60 higher)	-	⊕⊕○○ Low
Confirmed Unquantifiable										
3	serious ^a	not serious	not serious	serious ^f	none	140	152	SMD 0.27 lower (0.50 lower to 0.04 lower)	-	⊕⊕○○ Low
White matter volume (cm³) (m/SD)										
Very heavy PAE										
2	serious ^a	serious ^b	not serious	very serious ^{d,e,f}	none	22	18	SMD 0.12 lower (1.24 lower to 0.99 higher)	-	⊕○○○ Very Low
Left Hippocampus (mm³) (m/SD)										
Confirmed Unquantifiable										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	48	93	SMD 0.43 lower (0.78	-	⊕⊕○○ Low

								lower to 0.08 lower)		
Right Putamen (mm ³ or cm ³) (m/SD)										
Confirmed Unquantifiable										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	67	168	SMD 0.26 lower (0.73 lower to 0.20 higher)	-	⊕○○○ Very Low
Left Putamen (mm ³ or cm ³) (m/SD)										
Confirmed Unquantifiable										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	67	168	SMD 0.43 lower (0.86 lower to 0.00 lower)	-	⊕⊕○○ Low
Left Amygdala (mm ³) (m/SD)										
Confirmed Unquantifiable										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	48	89	SMD 0.30 lower (0.65 lower to 0.06 higher)	-	⊕○○○ Very Low
Right Amygdala (mm ³) (m/SD)										
Confirmed Unquantifiable										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	48	89	SMD 0.13 lower (0.48 lower to 0.23 higher)	-	⊕○○○ Very Low
Left Thalamus (mm ³) (m/SD)										
Confirmed Unquantifiable										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	48	89	SMD 0.27 lower (0.63 lower to 0.08 higher)	-	⊕○○○ Very Low
DIAGNOSED STUDIES										
Total brain/intracranial volume (cm ³) (m/SD)										
FASD										
6	serious ^a	not serious	not serious	not serious	none	277	275	SMD 0.61 lower (0.78 lower to 0.44 lower)	-	⊕⊕⊕○ Moderate
FAS/pFAS										
4	serious ^a	not serious	not serious	serious ^{e,f}	none	114	116	SMD 0.87 lower (1.29 lower to 0.44 lower)	-	⊕⊕○○ Low
ARND/Others										
2	serious ^a	not serious	not serious	serious ^{d,e,f}	none	46	35	SMD 0.28 lower (0.79 lower to 0.23 higher)	-	⊕⊕○○ Low
Right hippocampal volume (mm ³) (m/SD)										
FASD										
3	serious ^a	serious ^b	not serious	serious ^{e,f}	125	153	-	SMD 0.56 lower (1.04	-	⊕○○○ Very Low

								lower to 0.08 lower)		
FAS/pFAS										
3	serious ^a	not serious	serious ^c	serious ^{e,f}	57	36	-	SMD 0.64 lower (1.15 lower to 0.13 lower)	-	⊕○○○ Very Low
ARND/Others										
3	serious ^a	not serious	serious ^c	serious ^{e,f}	70	36	-	SMD 0.60 lower (0.96 lower to 0.25 lower)	-	⊕○○○ Very Low
Left hippocampal volume (mm ³) (m/SD)										
FASD										
4	serious ^a	not serious	not serious	serious ^{e,f}	134	172	-	SMD 0.60 lower (0.96 lower to 0.25 lower)	-	⊕⊕○○ Low
FAS/pFAS										
2	serious ^a	not serious	not serious	serious ^{e,f}	48	17	-	SMD 0.83 lower (1.49 lower to 0.18 lower)	-	⊕⊕○○ Low
ARND/Others										
2	serious ^a	not serious	serious ^c	serious ^{e,f}	70	36	-	SMD 0.70 lower (1.15 lower to 0.26 lower)	-	⊕○○○ Very Low
Total hippocampal volume (mm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^f	139	144	-	SMD 0.69 lower (0.93 lower to 0.45 lower)	-	⊕⊕○○ Low
ARND/Others										
3	serious ^a	serious ^b	not serious	very serious ^{d,e,f}	78	59	-	SMD 1.30 lower (2.62 lower to 0.03 higher)	-	⊕○○○ Very Low
Right caudate volume (mm ³) (m/SD)										
FAS/pFAS										
4	serious ^a	serious ^b	not serious	serious ^{e,f}	81	83	-	SMD 1.49 lower (2.45 lower to 0.52 lower)	-	⊕○○○ Very Low
ARND/Others										
2	serious ^a	serious ^b	not serious	serious ^{e,f}	48	17	-	SMD 1.05 lower (1.70 lower to 0.40 lower)	-	⊕○○○ Very Low
Left caudate volume (mm ³) (m/SD)										
FAS/pFAS										
4	serious ^a	serious ^b	not serious	serious ^{e,f}	54	110	-	SMD 1.03 lower (1.84	-	⊕○○○ Very Low

								lower to 0.21 lower)		
ARND/Others										
2	serious ^a	not serious	not serious	serious ^{e,f}	48	17	-	SMD 1.02 lower (1.66 lower to 0.37 lower)	-	⊕⊕○○ Low
Total caudate volume (mm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	139	144	-	SMD 0.88 lower (1.13 lower to 0.64 lower)	-	⊕⊕○○ Low
Total putamen volume (mm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	106	135	-	SMD 0.64 lower (1.00 lower to 0.28 lower)	-	⊕⊕○○ Low
Right putamen volume (mm ³) (m/SD)										
FASD										
2	serious ^a	serious ^b	not serious	serious ^{e,f}	106	135	-	SMD 0.96 lower (1.78 lower to 0.14 lower)	-	⊕○○○ Very Low
Left putamen volume (mm ³) (m/SD)										
FASD										
2	serious ^a	serious ^b	not serious	serious ^{e,f}	106	135	-	SMD 0.79 lower (1.29 lower to 0.29 lower)	-	⊕○○○ Very Low
Corpus callosum volume (mm ³) (m/SD)										
FAS/pFAS										
2	serious ^a	not serious	not serious	serious ^{e,f}	50	48	-	SMD 1.29 lower (1.83 lower to 0.76 lower)	-	⊕⊕○○ Low
Total grey matter volume (cm ³) (m/SD)										
FASD										
3	serious ^a	not serious	not serious	serious ^f	175	205	-	SMD 0.67 lower (0.88 lower to 0.46 lower)	-	⊕⊕○○ Low
Cortical grey matter volume (cm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	78	87	-	SMD 0.68 lower (0.99 lower to 0.36 lower)	-	⊕⊕○○ Low
Total subcortical grey matter volume (cm ³) (m/SD)										
FASD										
4	serious ^a	not serious	not serious	not serious	183	218	-	SMD 0.90 lower (1.13	-	⊕⊕⊕○ Moderate

								lower to 0.66 lower)		
Total white matter volume (cm ³) (m/SD)										
FASD										
4	serious ^a	serious ^b	not serious	very serious ^{d,e,f}	176	167	-	SMD 0.04 lower (0.65 lower to 0.57 higher)	-	⊕○○○ Very Low
Genu corpus callosum (FA) (m/SD)										
FASD										
3	serious ^a	not serious	not serious	serious ^f	146	128	-	SMD 0.42 lower (0.66 lower to 0.17 lower)	-	⊕⊕○○ Low
Rostral Body Corpus Callosum (FA) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	76	54	-	SMD 0.02 lower (0.37 lower to 0.33 higher)	-	⊕○○○ Very Low
Anterior Midbody Corpus Callosum (FA) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	76	54	-	SMD 0.00 (0.35 lower to 0.35 higher)	-	⊕○○○ Very Low
Posterior midbody corpus callosum (FA) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	76	54	-	SMD 0.44 lower (0.80 lower to 0.09 lower)	-	⊕⊕○○ Low
Isthmus corpus callosum (FA) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	76	54	-	SMD 0.45 lower (0.81 lower to 0.09 lower)	-	⊕⊕○○ Low
FAS/pFAS										
2	serious ^a	not serious	not serious	serious ^{e,f}	54	38	-	SMD 1.05 lower (1.76 lower to 0.34 lower)	-	⊕⊕○○ Low
Splenum corpus callosum (FA) (m/SD)										
FASD										
3	serious ^a	not serious	not serious	very serious ^{d,e,f}	146	128	-	SMD 0.18 lower (0.58 lower to 0.21 higher)	-	⊕○○○ Very Low
FAS/pFAS										
2	serious ^a	serious ^b	not serious	serious ^{e,f}	54	38	-	SMD 0.91 lower (1.74 lower to 0.07 lower)	-	⊕○○○ Very Low

ARND/Others										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	44	38	-	SMD 0.36 lower (0.80 lower to 0.08 higher)	-	⊕○○○ Very Low
Cerebellar grey matter (cm ³) (m/SD)										
FAS/pFAS										
2	serious ^a	not serious	not serious	serious ^{e,f}	80	67	-	SMD 1.12 lower (2.18 lower to 0.06 lower)	-	⊕⊕○○ Low
ARND/Others										
2	serious ^a	not serious	serious ^c	very serious ^{d,e,f}	74	67	-	SMD 0.40 lower (1.81 lower to 1.00 higher)	-	⊕○○○ Very Low
Cerebellar white matter (cm ³) (m/SD)										
FAS/pFAS										
2	serious ^a	not serious	not serious	serious ^{e,f}	80	67	-	SMD 1.19 lower (1.58 lower to 0.79 lower)	-	⊕⊕○○ Low
ARND/Others										
2	serious ^a	not serious	serious ^c	very serious ^{d,e,f}	74	67	-	SMD 0.65 lower (2.07 lower to 0.76 higher)	-	⊕○○○ Very Low
Left amygdala (cm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^f	106	135	-	SMD 0.57 lower (0.83 lower to 0.31 lower)	-	⊕⊕○○ Low
Right amygdala (cm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^f	106	135	-	SMD 0.50 lower (0.76 lower to 0.24 lower)	-	⊕⊕○○ Low
Left thalamus (cm ³) (m/SD)										
FASD										
2	serious ^a	serious ^b	not serious	serious ^{e,f}	106	135	-	SMD 0.83 lower (1.37 lower to 0.29 lower)	-	⊕○○○ Very Low
Right thalamus (cm ³) (m/SD)										
FASD										
2	serious ^a	serious ^b	not serious	serious ^{e,f}	106	135	-	SMD 0.86 lower (1.44 lower to 0.27 lower)	-	⊕○○○ Very Low
Thalamus (cm ³) (m/SD)										
FASD										

2	serious ^a	not serious	not serious	serious ^f	139	144	-	SMD 0.70 lower (0.94 lower to 0.46 lower)	-	⊕⊕○○ Low
Amygdala (cm ³) (m/SD)										
FASD										
2	serious ^a	not serious	not serious	serious ^f	139	144	-	SMD 0.25 lower (0.48 lower to 0.01 lower)	-	⊕⊕○○ Low

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

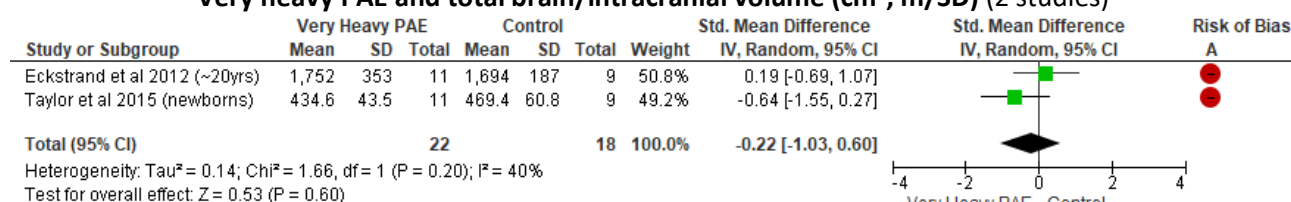
Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ($I^2 > 50\%$ and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) Wide 95% CIs for overall estimate; f) optimal information size criteria not met; g) While PAE and control group n's were not provided, the overall study sample size included in the data analysis = 47,178; h) One study provided sample size of 298.

Meta-analyses for quantitative MRI studies

Exposure Studies

Total brain/intracranial volume (cm³)

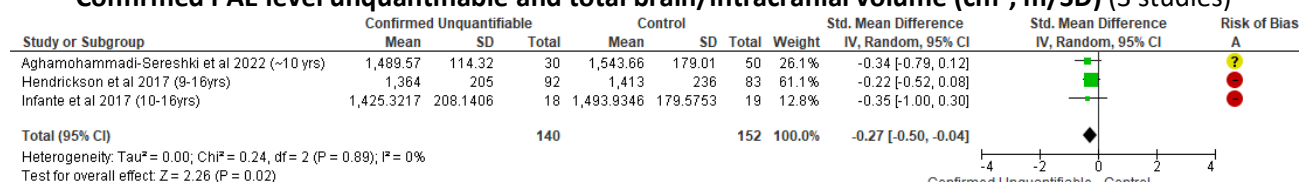
Very heavy PAE and total brain/intracranial volume (cm³, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

Confirmed PAE level unquantifiable and total brain/intracranial volume (cm³, m/SD) (3 studies)

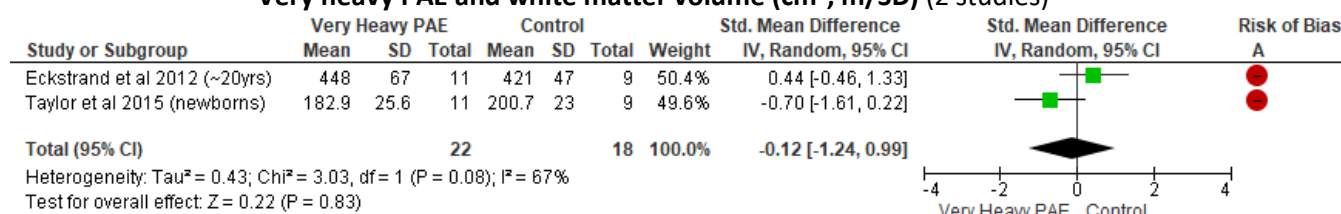


[Risk of bias legend](#)

(A) Overall RoB

White Matter Volume (cm³)

Very heavy PAE and white matter volume (cm³, m/SD) (2 studies)

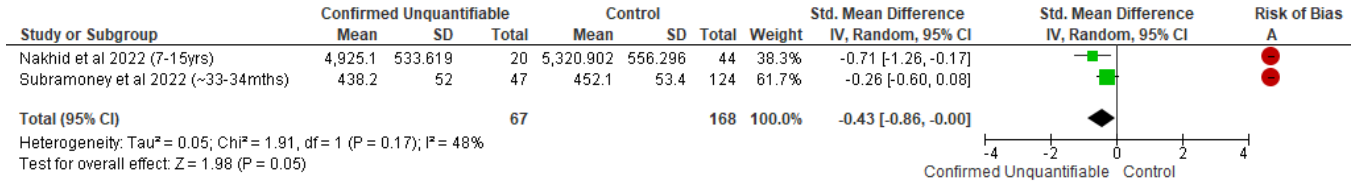


[Risk of bias legend](#)

(A) Overall RoB

Left Putamen Volume (cm³/mm³)

Confirmed PAE level unquantifiable and Left Putamen volume (cm/mm³) (m/SD)

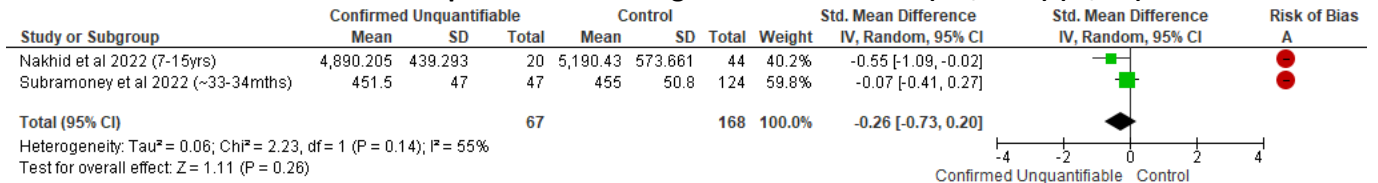


Risk of bias legend

(A) Overall RoB

Right Putamen Volume (cm³/mm³)

Confirmed PAE level unquantifiable and Right Putamen volume (cm/mm³) (m/SD)

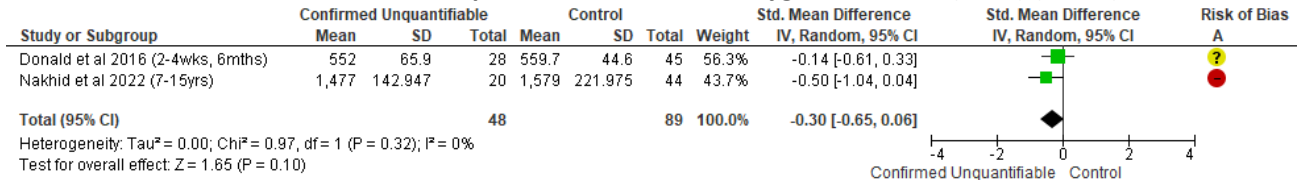


Risk of bias legend

(A) Overall RoB

Left Amygdala Volume (mm³)

Confirmed PAE level unquantifiable and Left Amygdala volume (mm³) (m/SD)

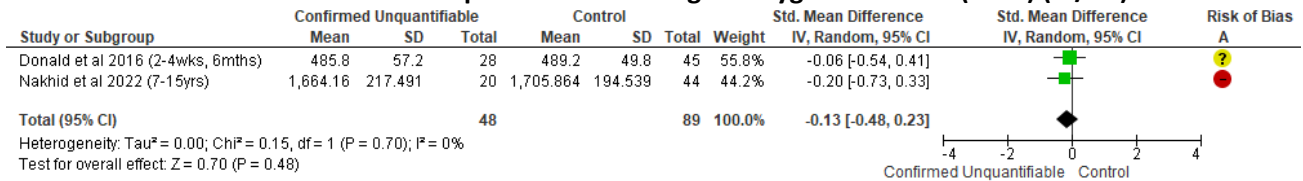


Risk of bias legend

(A) Overall RoB

Right Amygdala Volume (mm³)

Confirmed PAE level unquantifiable and Right Amygdala volume (mm³) (m/SD)

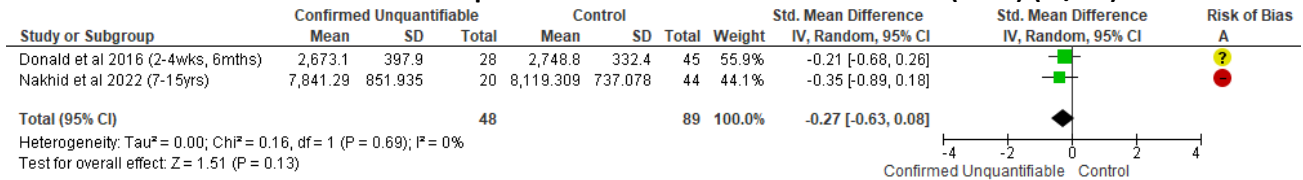


Risk of bias legend

(A) Overall RoB

Left Thalamus Volume (mm³)

Confirmed PAE level unquantifiable and Left Thalamus volume (mm³) (m/SD)

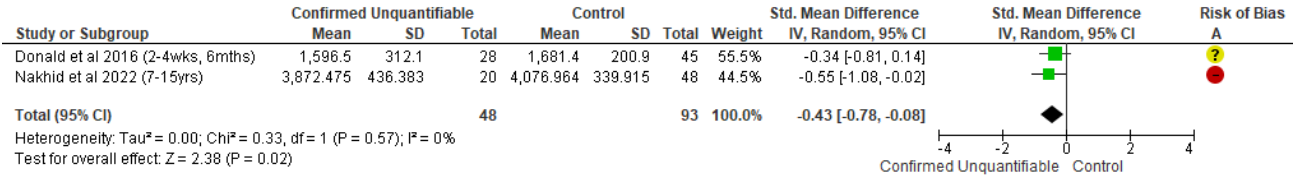


Risk of bias legend

(A) Overall RoB

Left Hippocampus Volume (mm³)

Confirmed PAE level unquantifiable and Left Hippocampus volume (mm³) (m/SD)



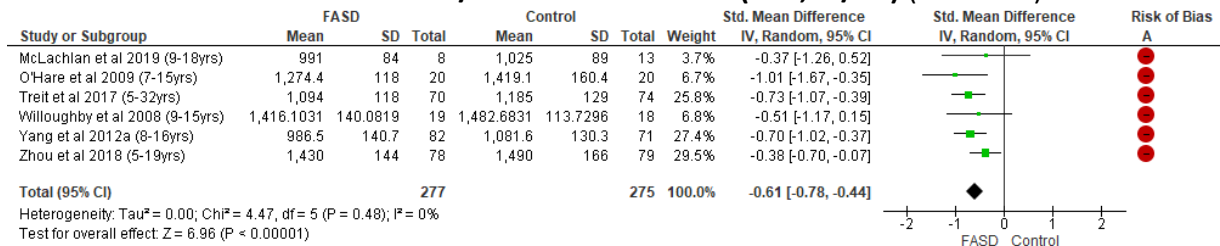
[Risk of bias legend](#)

(A) Overall RoB

Diagnosed Studies

Total brain/intracranial volume (cm³)

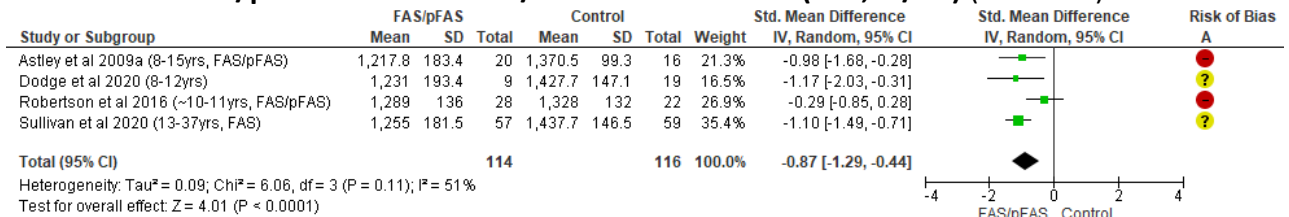
FASD and total brain/intracranial volume (cm³, m/SD) (6 studies)



[Risk of bias legend](#)

(A) Overall RoB

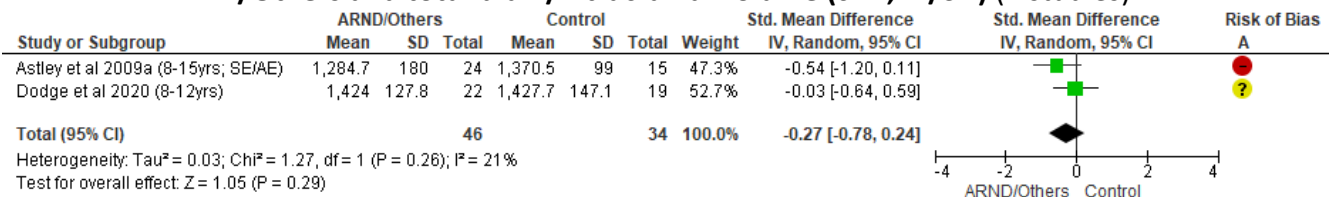
FAS/pFAS and total brain/intracranial volume (cm³, m/SD) (4 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and total brain/intracranial volume (cm³, m/SD) (2 studies)

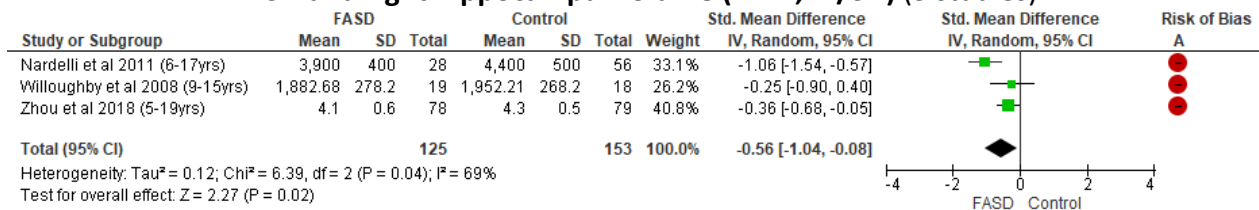


[Risk of bias legend](#)

(A) Overall RoB

Right hippocampal volume (mm³)

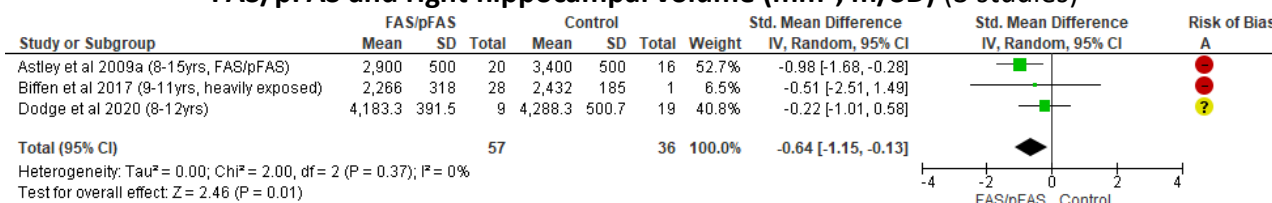
FASD and right hippocampal volume (mm³, m/SD) (3 studies)



[Risk of bias legend](#)

(A) Overall RoB

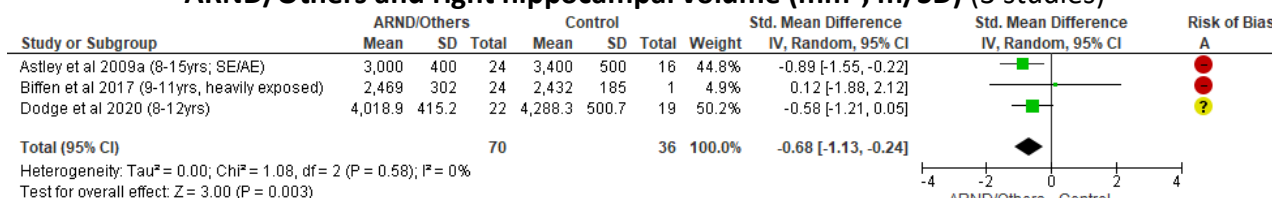
FAS/pFAS and right hippocampal volume (mm³, m/SD) (3 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and right hippocampal volume (mm³, m/SD) (3 studies)

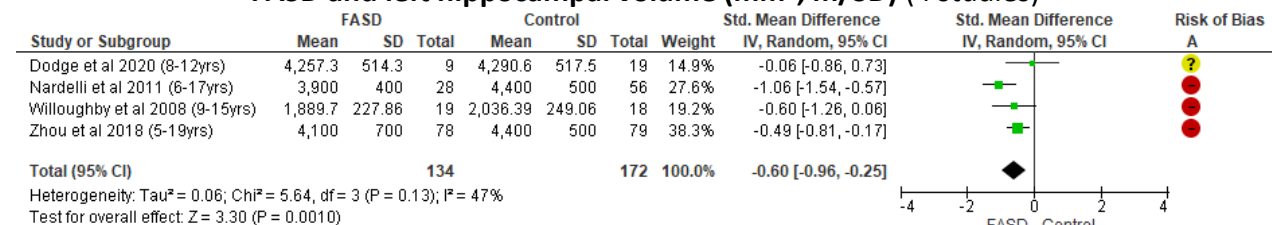


[Risk of bias legend](#)

(A) Overall RoB

Left hippocampal volume (mm³)

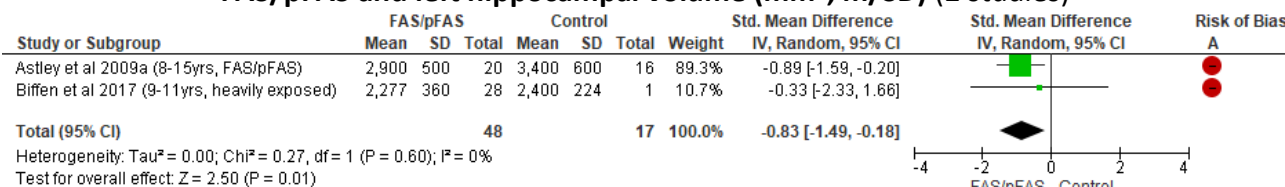
FASD and left hippocampal volume (mm³, m/SD) (4 studies)



[Risk of bias legend](#)

(A) Overall RoB

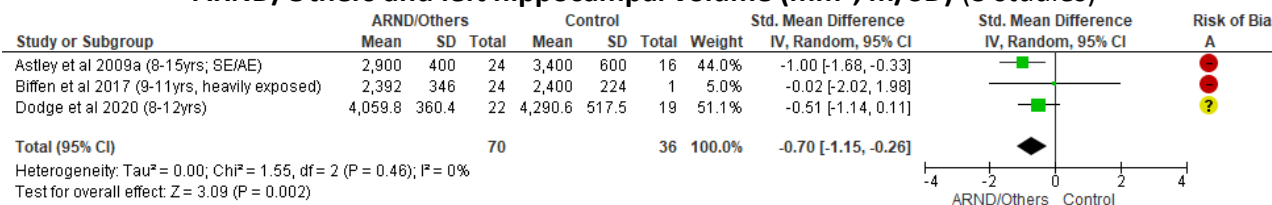
FAS/pFAS and left hippocampal volume (mm³, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and left hippocampal volume (mm³, m/SD) (3 studies)

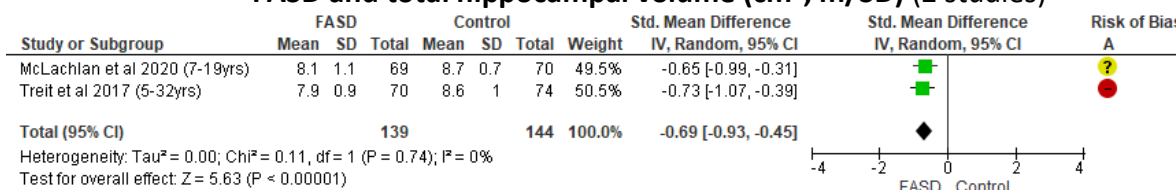


[Risk of bias legend](#)

(A) Overall RoB

Total hippocampal volume (cm³)

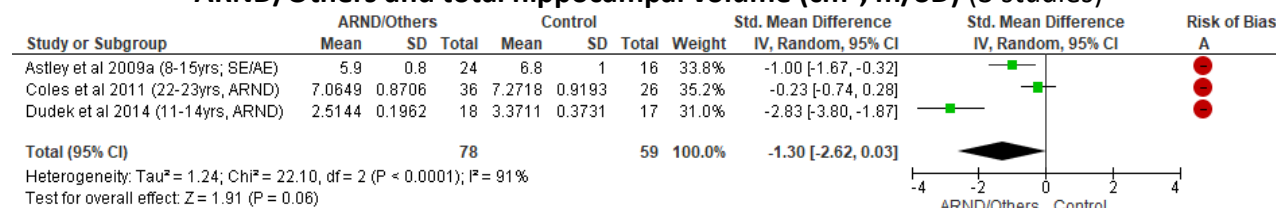
FASD and total hippocampal volume (cm³, m/SD) (2 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and total hippocampal volume (cm³, m/SD) (3 studies)

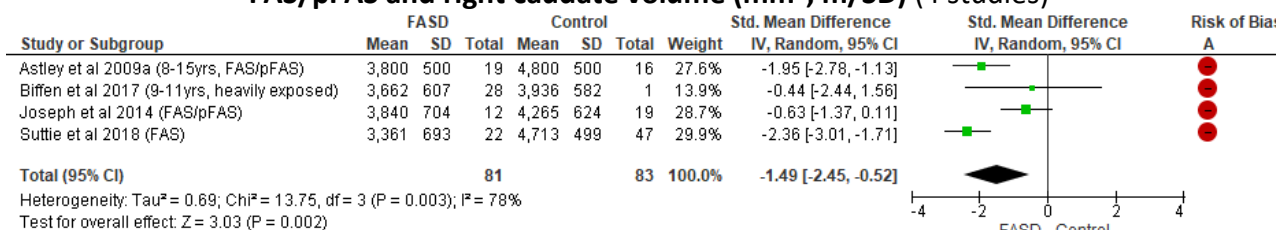


Risk of bias legend

(A) Overall RoB

Right caudate volume (mm³)

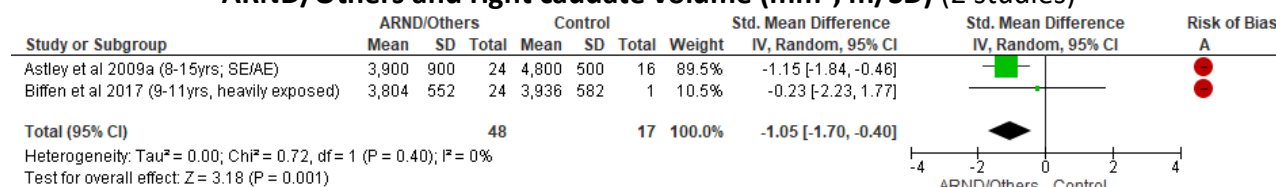
FAS/pFAS and right caudate volume (mm³, m/SD) (4 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and right caudate volume (mm³, m/SD) (2 studies)

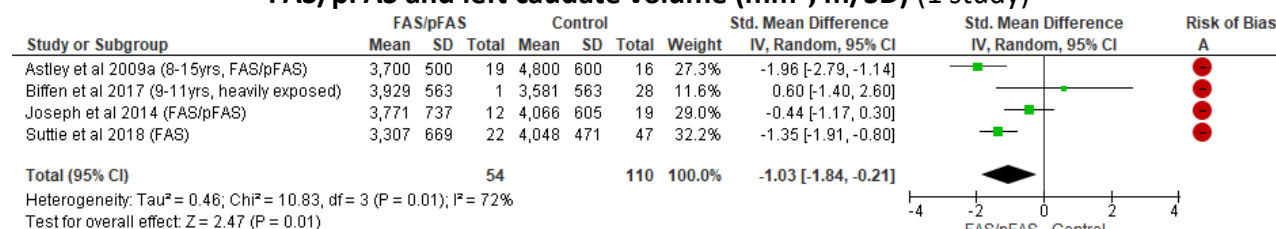


Risk of bias legend

(A) Overall RoB

Left caudate volume (mm³)

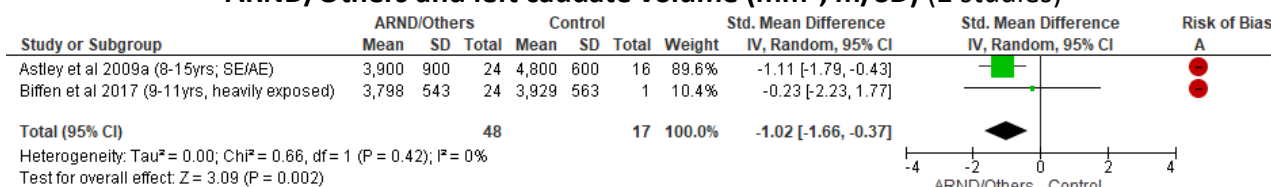
FAS/pFAS and left caudate volume (mm³, m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

ARND/Others and left caudate volume (mm³, m/SD) (2 studies)

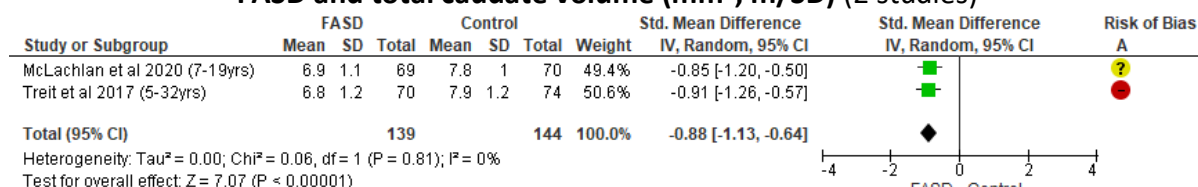


[Risk of bias legend](#)

(A) Overall RoB

Total caudate volume (mm³)

FASD and total caudate volume (mm³, m/SD) (2 studies)

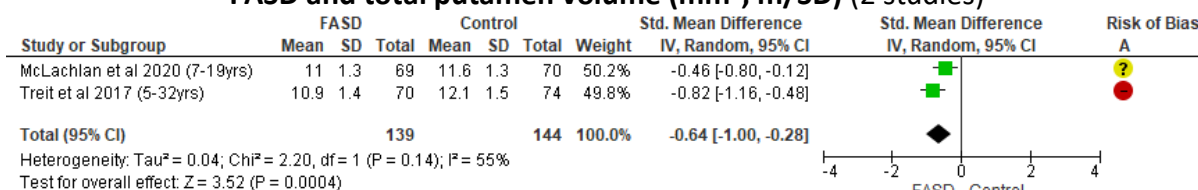


[Risk of bias legend](#)

(A) Overall RoB

Total putamen volume (mm³)

FASD and total putamen volume (mm³, m/SD) (2 studies)

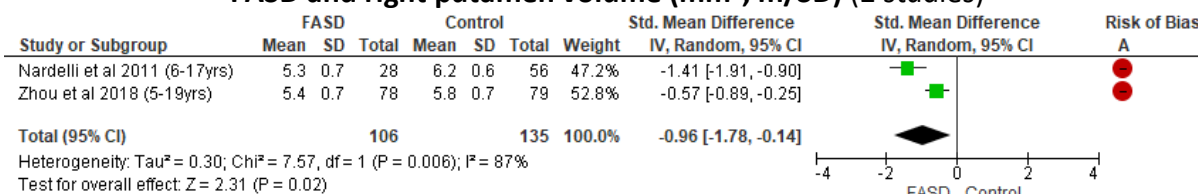


[Risk of bias legend](#)

(A) Overall RoB

Right putamen volume (mm³)

FASD and right putamen volume (mm³, m/SD) (2 studies)

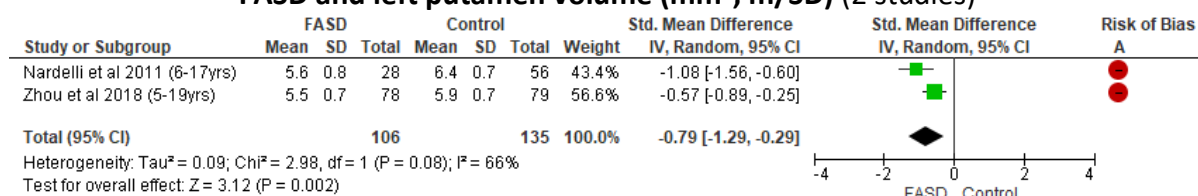


[Risk of bias legend](#)

(A) Overall RoB

Left putamen volume (mm³)

FASD and left putamen volume (mm³, m/SD) (2 studies)

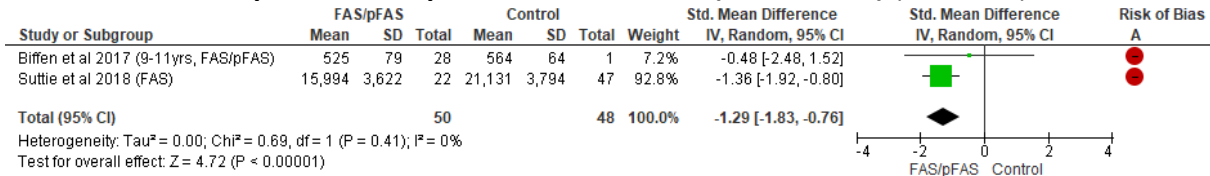


[Risk of bias legend](#)

(A) Overall RoB

Corpus callosum volume (mm³)

FAS/pFAS and corpus callosum volume (mm³, m/SD) (2 studies)

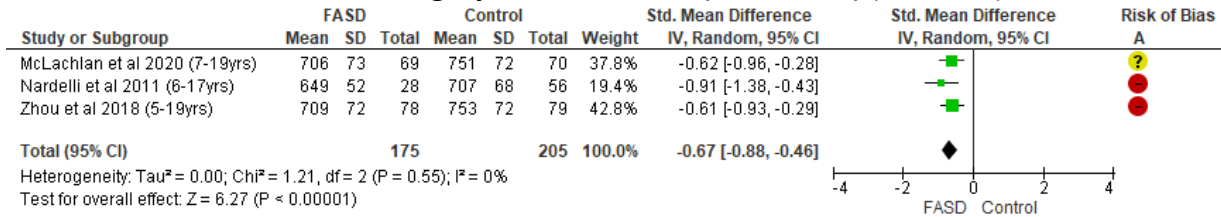


[Risk of bias legend](#)

(A) Overall RoB

Total Grey Matter Volume (cm³)

FASD and total grey matter volume (cm³, m/SD) (3 studies)

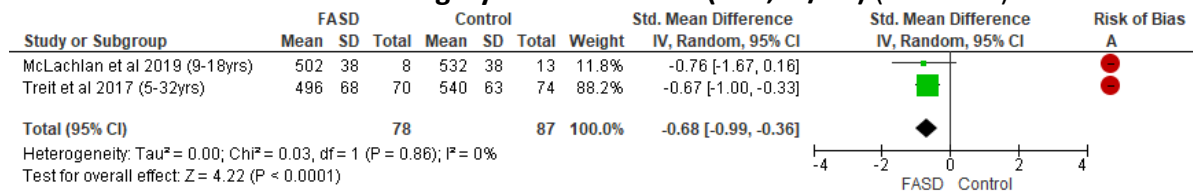


[Risk of bias legend](#)

(A) Overall RoB

Cortical Grey Matter Volume (cm³)

FASD and cortical grey matter volume (cm³, m/SD) (2 studies)

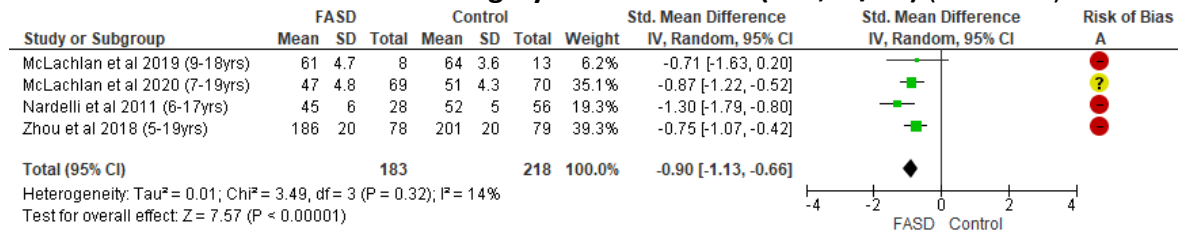


[Risk of bias legend](#)

(A) Overall RoB

Total Subcortical Grey Matter Volume (cm³)

FASD and total subcortical grey matter volume (cm³, m/SD) (4 studies)

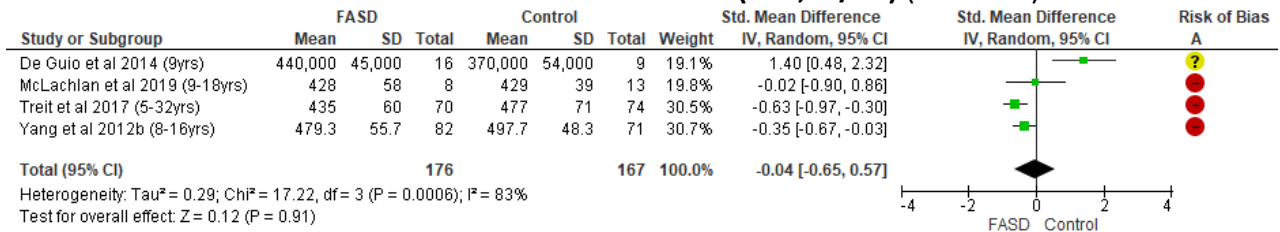


[Risk of bias legend](#)

(A) Overall RoB

Total White Matter Volume (cm³)

FASD and total white matter volume (cm³, m/SD) (4 studies)

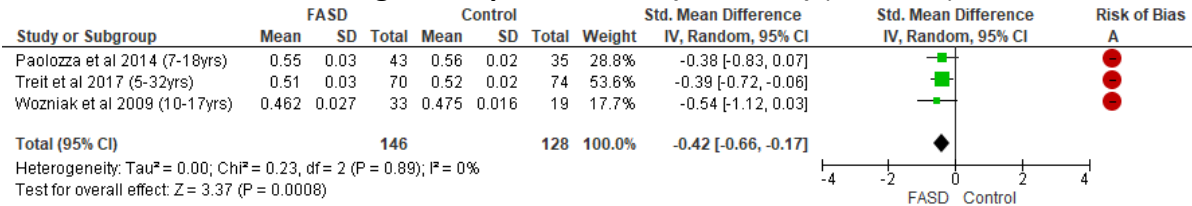


[Risk of bias legend](#)

(A) Overall RoB

Genu Corpus Callosum (FA)

FASD and genu corpus callosum (FA, m/SD) (3 studies)

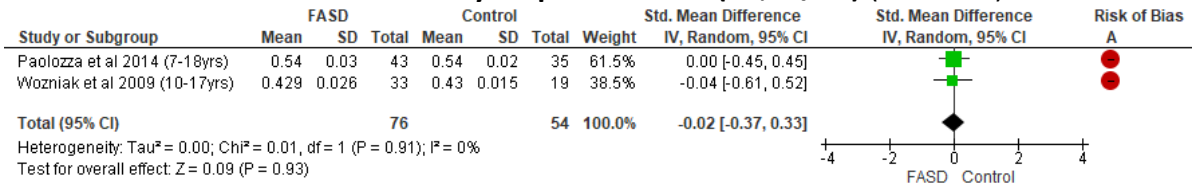


[Risk of bias legend](#)

(A) Overall RoB

Rostral Body Corpus Callosum (FA)

FASD and rostral body corpus callosum (FA, m/SD) (2 studies)

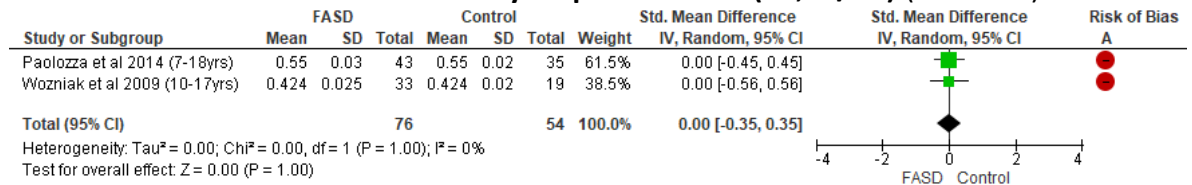


[Risk of bias legend](#)

(A) Overall RoB

Anterior Midbody Corpus Callosum (FA)

FASD and anterior midbody corpus callosum (FA, m/SD) (2 studies)

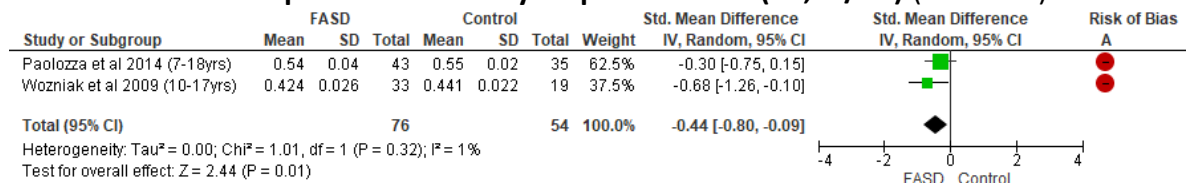


[Risk of bias legend](#)

(A) Overall RoB

Posterior Midbody Corpus Callosum (FA)

FASD and posterior midbody corpus callosum (FA, m/SD) (2 studies)

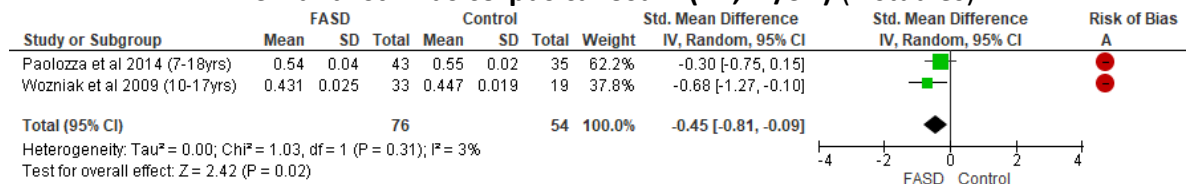


[Risk of bias legend](#)

(A) Overall RoB

Isthmus Corpus Callosum (FA)

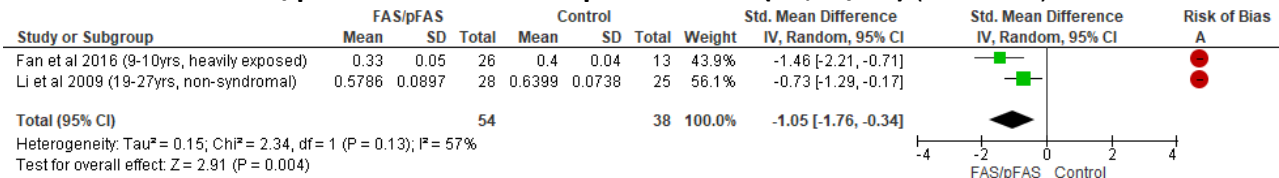
FASD and isthmus corpus callosum (FA, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

FAS/pFAS and Isthmus corpus callosum (FA, m/SD) (2 studies)

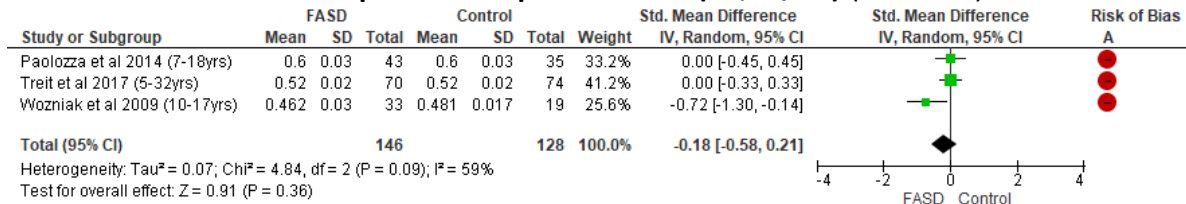


[Risk of bias legend](#)

(A) Overall RoB

Splenium Corpus Callosum (FA)

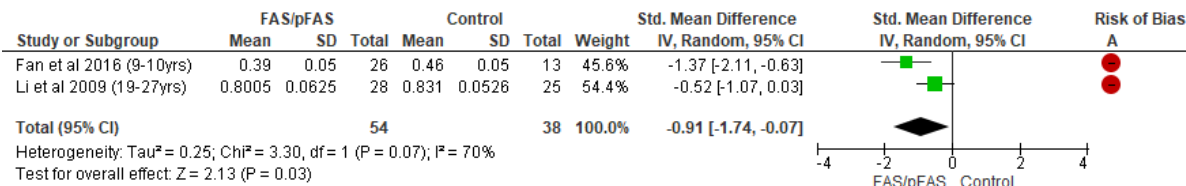
FASD and splenium corpus callosum (FA, m/SD) (3 studies)



[Risk of bias legend](#)

(A) Overall RoB

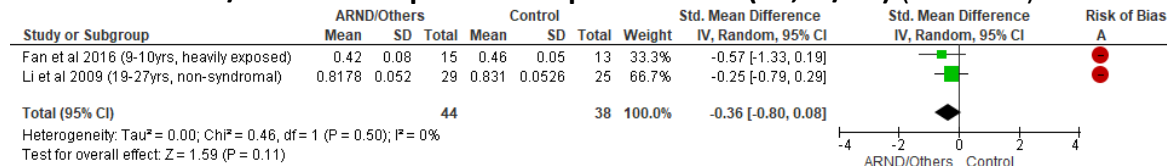
FAS/pFAS and splenium corpus callosum (FA, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and splenium corpus callosum (FA, m/SD) (2 studies)

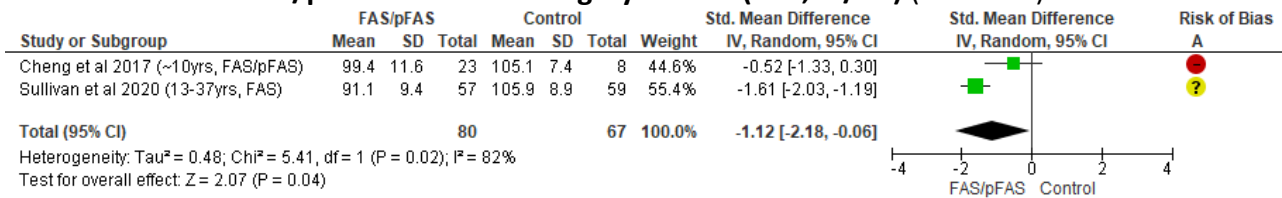


[Risk of bias legend](#)

(A) Overall RoB

Cerebellar grey matter (cm³)

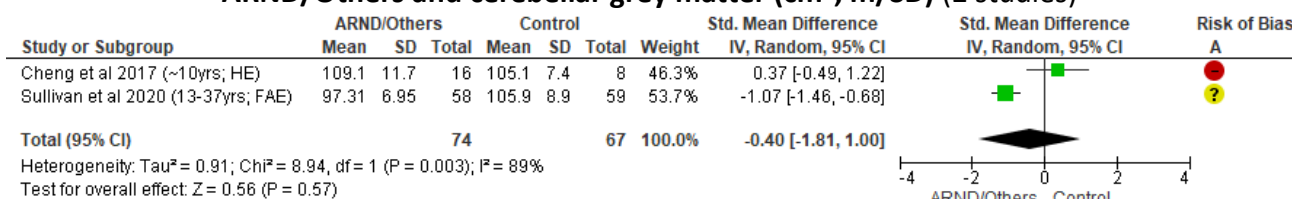
FAS/pFAS and cerebellar grey matter (cm³, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and cerebellar grey matter (cm³, m/SD) (2 studies)

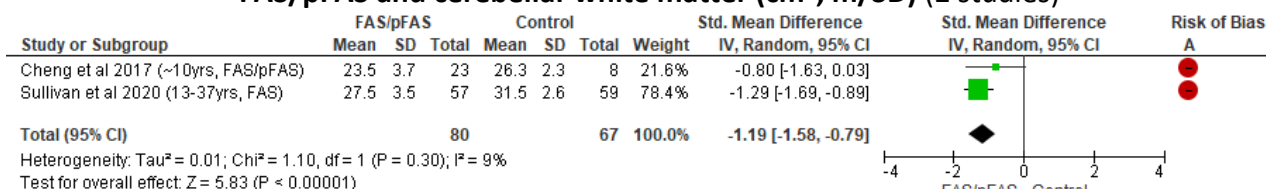


[Risk of bias legend](#)

(A) Overall RoB

Cerebellar white matter (cm³)

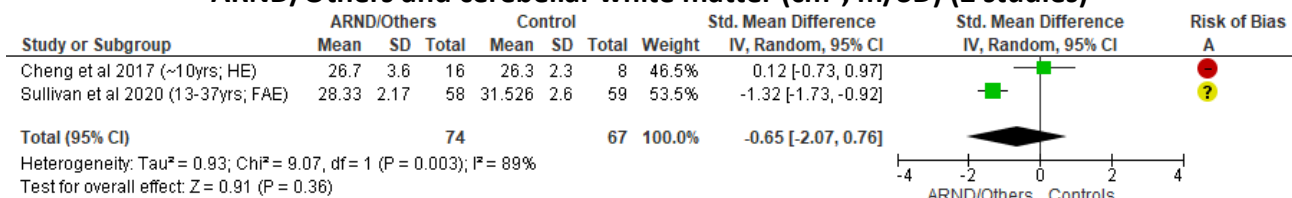
FAS/pFAS and cerebellar white matter (cm³, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and cerebellar white matter (cm³, m/SD) (2 studies)

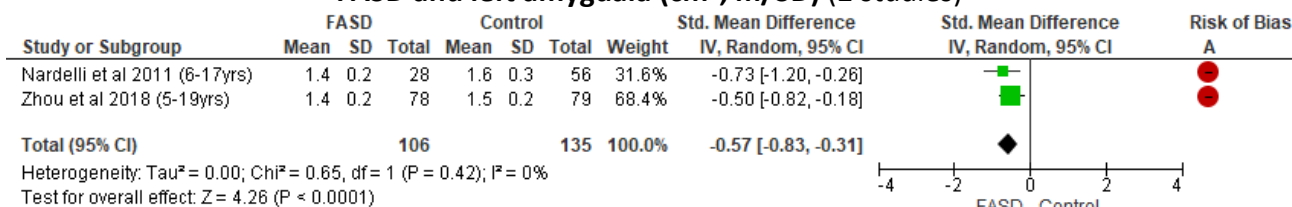


[Risk of bias legend](#)

(A) Overall RoB

Left amygdala (cm³)

FASD and left amygdala (cm³, m/SD) (2 studies)

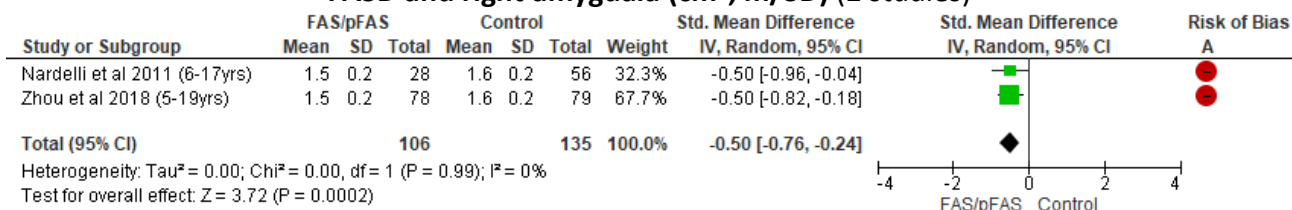


[Risk of bias legend](#)

(A) Overall RoB

Right amygdala (cm³)

FASD and right amygdala (cm³, m/SD) (2 studies)

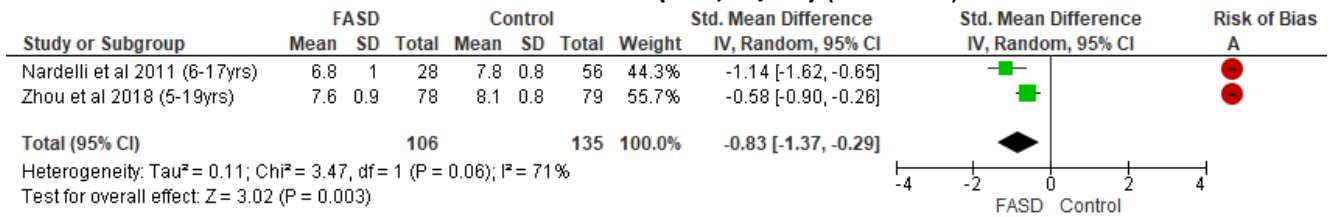


[Risk of bias legend](#)

(A) Overall RoB

Left thalamus (cm³)

FASD and left thalamus (cm³, m/SD) (2 studies)

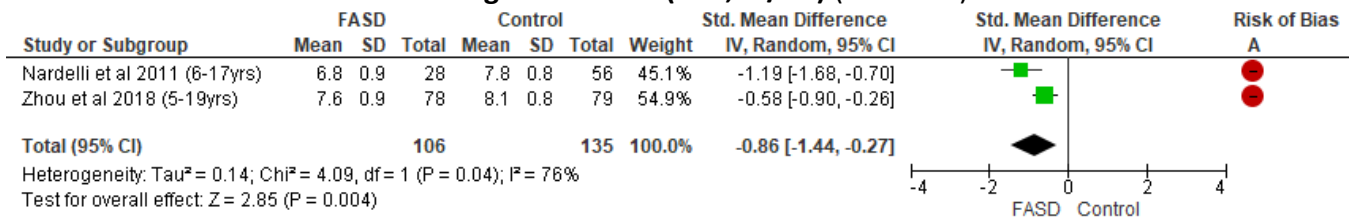


[Risk of bias legend](#)

(A) Overall RoB

Right thalamus (cm³)

FASD and right thalamus (cm³, m/SD) (2 studies)

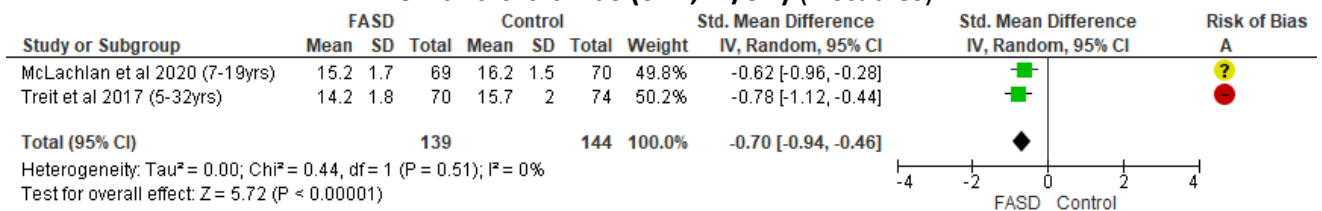


[Risk of bias legend](#)

(A) Overall RoB

Thalamus (cm³)

FASD and thalamus (cm³, m/SD) (2 studies)

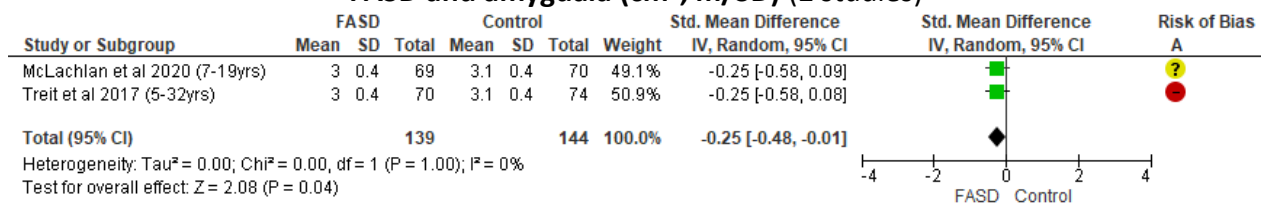


[Risk of bias legend](#)

(A) Overall RoB

Amygdala (cm³)

FASD and amygdala (cm³, m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

Summary of available outcomes for seizures

Seizures			
Study Type	Outcome	Data	# of studies
Exposure	Risk of neonatal seizures & risk of epilepsy	Adjusted incident rate ratios	1 study: 1 Light, 1 Moderate and, 1 Binge exposure

*adjusted for maternal age, gestational age, parity, household SES, prenatal smoking, maternal hx of epilepsy & time to pregnancy

GRADE ratings for seizures

	Certainty assessment					№ of patients		Effect		Certainty
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Risk of neonatal seizures										
≥ 1 binge at 11-16 weeks										
1	not serious	not serious	not serious	serious ^{e,f}	none	6/1,2 63	123/76, 685	aIRR 3.15 (1.37 to 7.25)	-	⊕⊕⊕○ Moderate
Light PAE										
1	not serious	not serious	not serious	serious ^d	none	722/ 36,07 5	700/34, 997	aIRR 0.75 (0.5 to 1.12)	-	⊕⊕⊕○ Moderate
Moderate PAE										
1	not serious	not serious	not serious	serious ^{d,e}	none	210/ 20,95 5	700/34, 997	aIRR 1.08 (0.34 to 3.45)	-	⊕⊕⊕○ Moderate
Risk of Epilepsy										
≥ 1 binge at 11-16 weeks										
1	not serious	not serious	not serious	not serious	none	19/1, 262	541/76, 543	aIRR 1.81 (1.13 to 2.90)	-	⊕⊕⊕○ Moderate
Light PAE										
1	not serious	not serious	not serious	serious ^d	none	2,165 /36,0 75	2,800/3 4,997	aIRR 0.91 (0.76 to 1.10)	-	⊕⊕⊕○ Moderate
Moderate PAE										
1	not serious	not serious	not serious	serious ^d	none	1,467 /20,9 55	2,800/3 4,997	aIRR 0.54 (0.25 to 1.14)	-	⊕⊕⊕○ Moderate

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ($I^2 > 50\%$ and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) wide 95% CI; f) optimal information size criteria were not met.

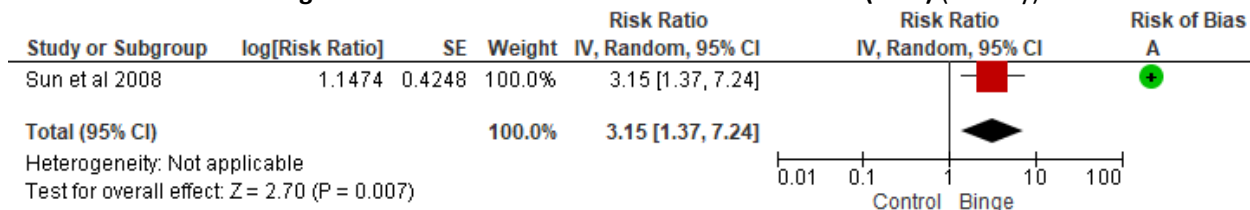
Additional Note: Sun et al 2008 reported 2 measures of 'moderate PAE'. Used higher PAE.

Meta-analyses for seizures

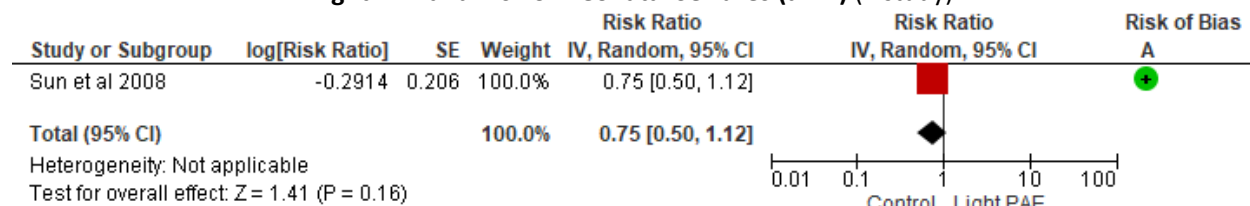
Exposure studies

Neonatal Seizure Risk (aIRR)

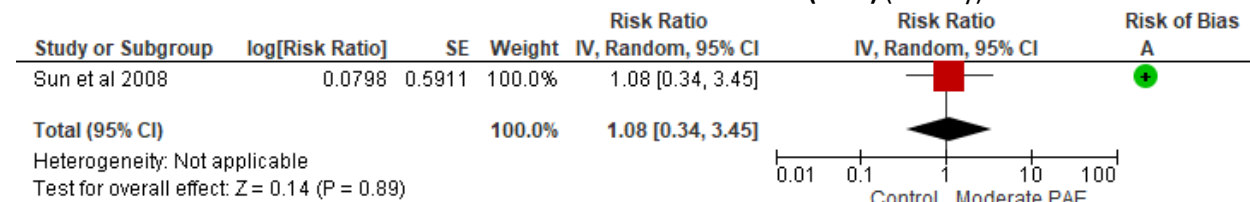
≥1 Binge at 11-16 weeks and Risk of Neonatal Seizures (aIRR) (1 study)



Light PAE and Risk of Neonatal Seizures (aIRR) (1 study)

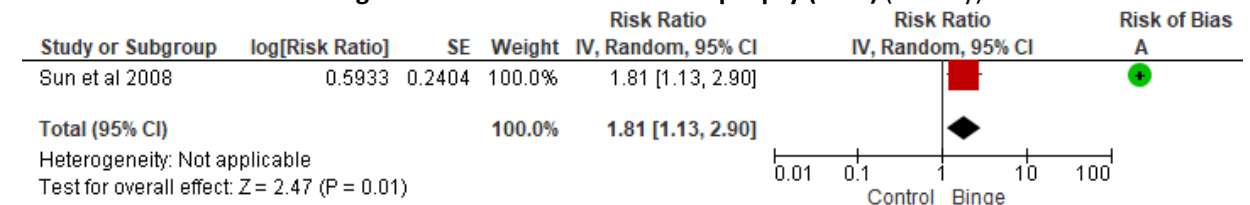


Moderate PAE and Risk of Neonatal Seizures (aIRR) (1 study)

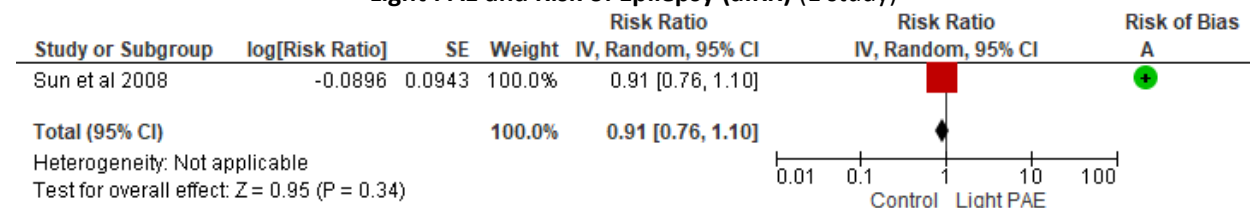


Epilepsy Risk (aIRR)

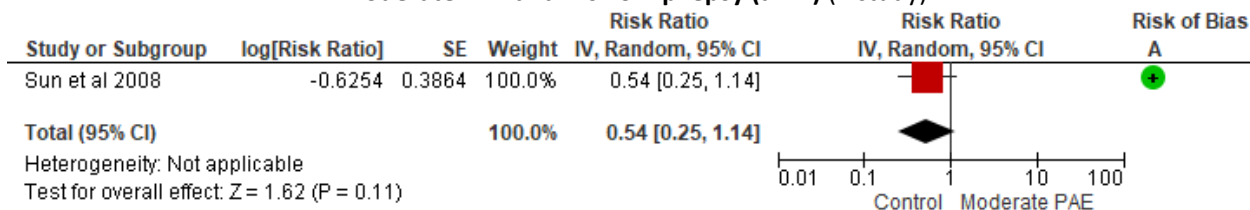
≥1 Binge at 11-16 weeks and Risk of Epilepsy (aIRR) (1 study)



Light PAE and Risk of Epilepsy (aIRR) (1 study)



Moderate PAE and Risk of Epilepsy (aIRR) (1 study)



Summary of available outcomes for cerebral palsy

Cerebral palsy			
Study Type	Outcome	Data	# of studies
Exposure	Pre/perinatal acquired CP	Adjusted ORs*	1 confirmed unquantified
	All CP types	Unadjusted ORs	1 confirmed unquantified

*adjusted for term births, Aboriginal status (outcome here non-Aboriginal only), appropriate fetal growth, illicit drug use. Other potential confounders examined and not found to be influence results: marital status, parity, SES, pregnancy complications, smoking.

GRADE ratings for cerebral palsy

Certainty assessment					№ of patients		Effect		Certainty
Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
E STUDIES									
Perinatal acquired CP									
Confirmed unquantified									
serious ^a	not serious	not serious	serious ^e	none	13,807	40,148	aOR 3.32 (1.30 to 8.48)	-	⊕⊕○○ Low
All CP types									
Confirmed unquantified									
serious ^a	not serious	not serious	not serious	none	13,969	40,302	OR 1.78 (1.28 to 2.46)	-	⊕⊕⊕○ Moderate

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ($I^2 > 50\%$ and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) cwide 95%; f) optimal information size criteria were not met.

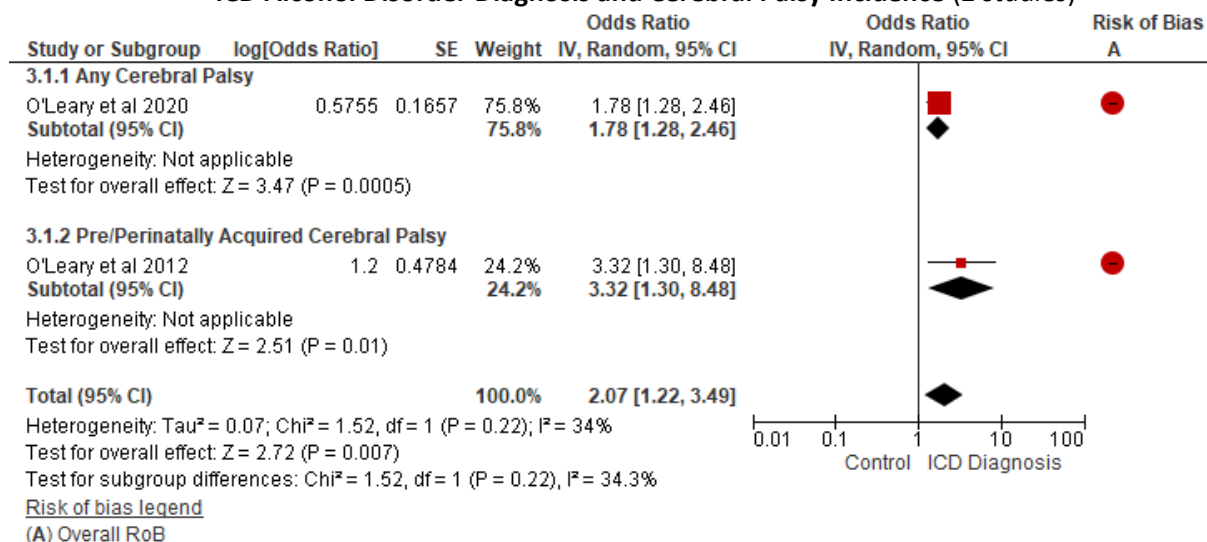
Additional Note: Both O'Leary 2012 and O'Leary 2020 used an ICD-9/10 diagnosis as the inclusion criteria for their exposure group, therefore the control group may include women who drank to a lesser extent in pregnancy. We chose to report these studies as these were the only studies found examining PAE and cerebral palsy.

Meta-analyses for cerebral palsy

Exposure studies

Cerebral Palsy Diagnosis

ICD Alcohol Disorder Diagnosis and Cerebral Palsy Incidence (2 studies)



Summary of available outcomes for visual impairment

Visual Impairment			
Study Type	Outcome	Data	# of studies
Exposure	Severe visual acuity (0.1 to < 0.5)	Frequency	1 study: Very Heavy PAE
	Abnormal visual abilities ^a	Frequency	1 study: Light, Moderate, Heavy PAE
Diagnosed	Visual acuity ≤ 0.2	Frequency	1 study: FAS

^a not defined

GRADE ratings for visual impairment

	Certainty assessment					№ of patients		Effect		Certainty
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Frequency of Severe Visual Acuity (0.1 to <0.5)										
Very Heavy PAE										
1	serious ^a	not serious	serious ^c	very serious ^{d,e,f}	none	43	55	OR 1.29 (0.08 to 21.16)	-	⊕○○○ Very Low
Frequency of Abnormal Visual Abilities										
Light PAE										
1	serious ^a	not serious	not serious	serious ^{d,f}	none	18/675	19/758	OR 1.07 (0.55 to 2.05)	-	⊕⊕○○ Low
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	8/175	19/758	OR 1.86 (0.80 to 4.33)	-	⊕○○○ Very Low
Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	2/20	19/758	OR 4.32 (0.94 to 19.96)	-	⊕○○○ Very Low
DIAGNOSED STUDIES										
Frequency of Visual Acuity (<2.0)										
FAS										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	-	4/30	0/22	OR 7.64 (0.39 to 149.74)	-	⊕○○○ Very Low

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio

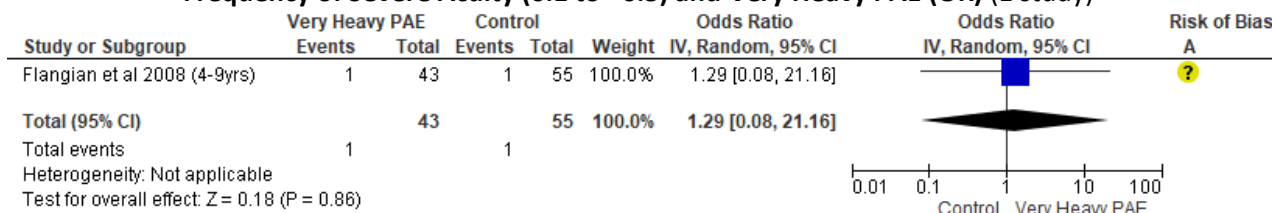
Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity (I^2 >50% and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) wide 95% CI for overall estimate; f) optimal information size criteria were not met.

Meta-analyses for visual impairment

Exposure studies

Visual Acuity (Frequency/OR)

Frequency of Severe Acuity (0.1 to <0.5) and Very Heavy PAE (OR) (1 study)

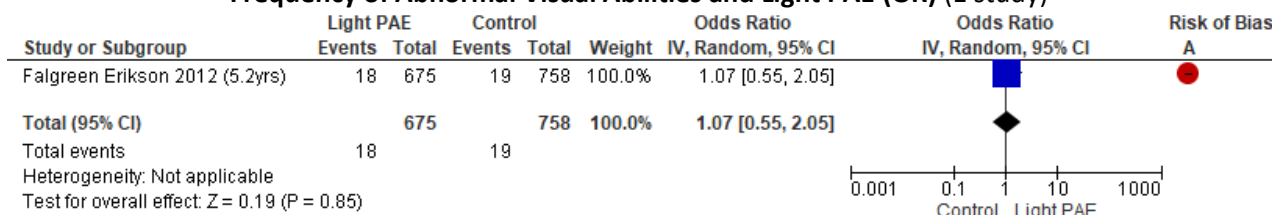


[Risk of bias legend](#)

(A) Overall RoB

Abnormal Visual Abilities (Frequency/OR)

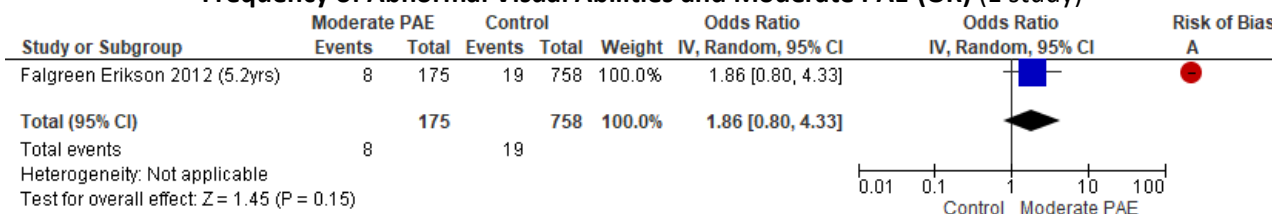
Frequency of Abnormal Visual Abilities and Light PAE (OR) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

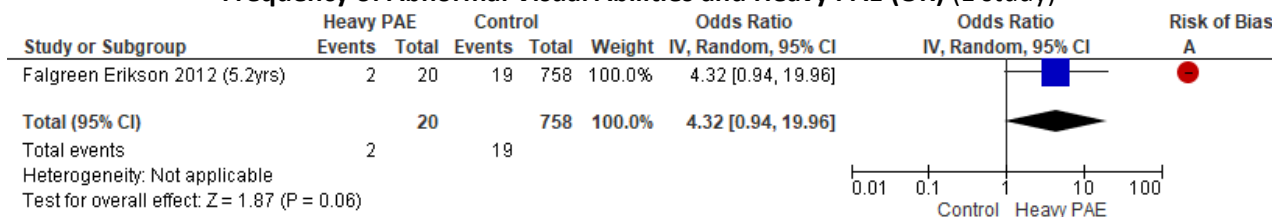
Frequency of Abnormal Visual Abilities and Moderate PAE (OR) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

Frequency of Abnormal Visual Abilities and Heavy PAE (OR) (1 study)



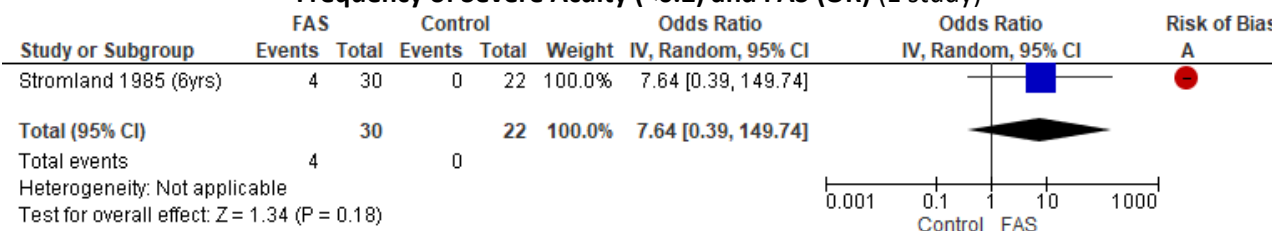
[Risk of bias legend](#)

(A) Overall RoB

Diagnosed studies

Visual Acuity (Frequency/OR)

Frequency of Severe Acuity (<0.2) and FAS (OR) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

Summary of available outcomes for hearing loss

Hearing loss			
Study Type	Outcome	Data	# of studies
Exposure	Abnormal hearing abilities ^a	Frequency	1 study: 1 Light, Moderate, Heavy PAE
	Hearing impairment ^b	Adjusted ORs ^c	1 study: Any PAE

^a not defined

^b defined as children receiving medical treatment for hearing impairment congenital or definitive cases of hearing impairment

^c adjusted for child sex, birth order, birth weight, history of otitis media, mothers age at pregnancy, familial history of hearing impairment, prenatal smoking

GRADE ratings for hearing loss

	Certainty assessment					№ of patients		Effect		Certainty
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Frequency of abnormal hearing abilities										
Light										
1	serious ^a	not serious	not serious	serious ^f	none	40/675	28/785	OR 1.7 (1.04 to 2.79)	-	⊕⊕○○ Low
Moderate										
1	serious ^a	not serious	not serious	serious ^{d,f}	none	7/175	28/785	OR 1.13 (0.48 to 2.26)	-	⊕⊕○○ Low
Heavy										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	3/20	28/785	OR 4.77 (1.32 to 17.23)	-	⊕○○○ Very Low
Hearing impairment (aOR)										
Any PAE										
1	serious ^a	not serious	serious ^c	serious ^{d,e}	none	10,562		aOR 1.49 (0.75 to 2.96)	-	⊕○○○ Very Low

Notes: CI: confidence interval; MD: mean difference; OR: odds ratio; aOR: adjusted odds ratio

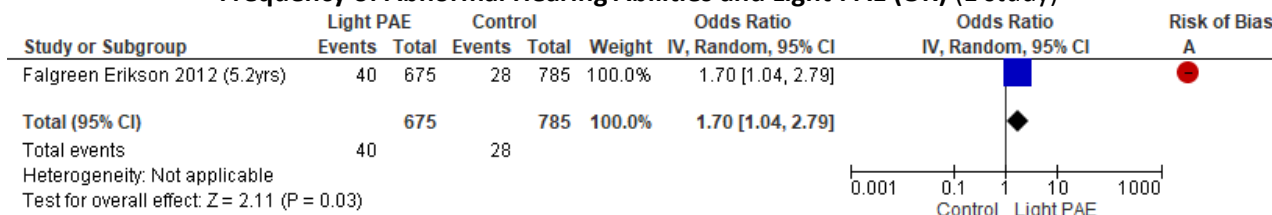
Explanations: a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ($I^2 > 50\%$ and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no effect; e) Wide 95% CI; f) optimal information size criteria were not met.

Meta-analyses for hearing loss

Exposure studies

Abnormal Hearing Ability (Frequency/OR)

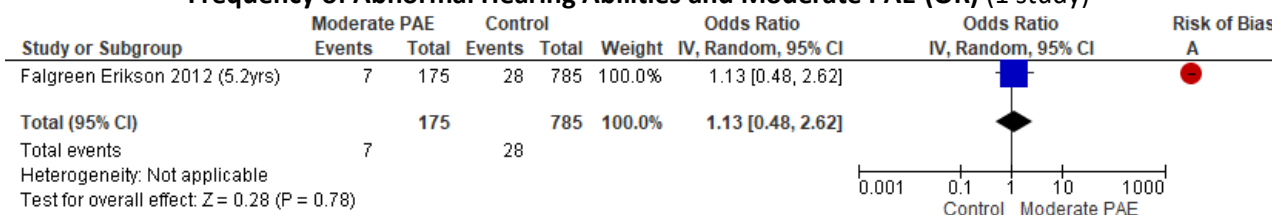
Frequency of Abnormal Hearing Abilities and Light PAE (OR) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

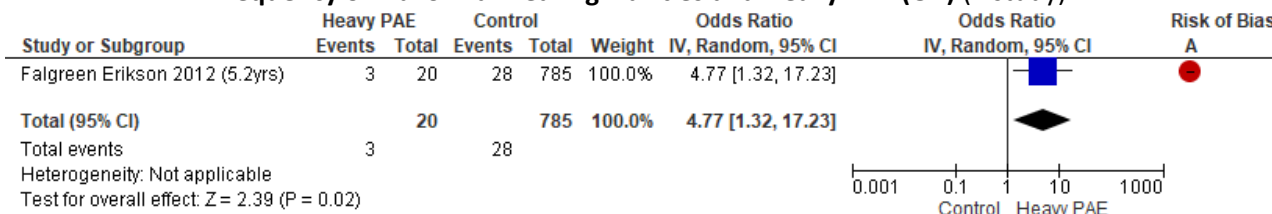
Frequency of Abnormal Hearing Abilities and Moderate PAE (OR) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

Frequency of Abnormal Hearing Abilities and Heavy PAE (OR) (1 study)

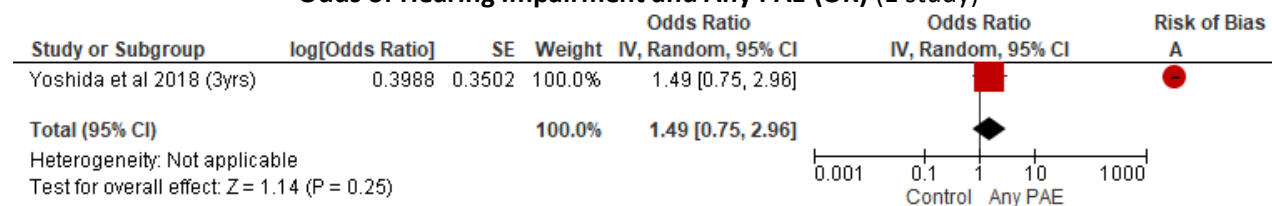


[Risk of bias legend](#)

(A) Overall RoB

Hearing Impairment (OR)

Odds of Hearing Impairment and Any PAE (OR) (1 study)



[Risk of bias legend](#)

(A) Overall RoB