## 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-	Head Circumference at Birth ≤10 <sup>th</sup> percentile	aOR and 95% CIs or number of cases with event (grouped together for unadj OR)	<b>2 studies:</b> 1 light, 1 moderate, 0 heavy, 1 very heavy, 0 any, 0 confirmed-unquantifiable								
unquantifiable)	Head Circumference at Birth ≤3 <sup>rd</sup> 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	<b>3 studies:</b> 1 light, 1 moderate, 1 heavy, 2 very heavy, 0 any, 0 confirmedunquantifiable								
Exposure Studies (light, moderate, heavy, very heavy, any level, confirmed-	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								
unquantifiable)	Postnatal Head Circumference ≤10 <sup>th</sup> 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	<b>1 study:</b> 1 heavy								
<b>Diagnosed Studies</b> (FASD, FAS, pFAS,	Head Circumference at Birth	Mean and SDs	<b>4 studies:</b> 0 FASD, 0 FAS, 3 pFAS, 3 Other								
Other FASDs)	Postnatal Head Circumference (6-9 yrs)	Mean and SDs	<b>14 studies</b> : 4 FASD, 7 FAS, 5 pFAS, 3 Other								
(3yrs – 22 yrs)	Postnatal Head Circumference (9-18 yrs)	Mean and SDs	<b>4 studies:</b> 1 FASD, 2 FAS, 2 pFAS, 4 Other								
	Postnatal Head Circumference Centiles	Mean and SDs	<b>9 studies:</b> 0 FASD, 6 FAS, 8 pFAS, 7 Other								
	Postnatal Head Circumference ≤3 <sup>rd</sup> percentile	% or number of cases with event (grouped together for unadj OR)	<b>6 studies:</b> 1 FASD, 4 FAS, 4 pFAS,4 Other								
	Postnatal Head Circumference ≤10 <sup>th</sup> percentile	% or number of cases with event (grouped together for unadj OR)	<b>8 studies:</b> 2 FASD, 6 FAS, 5 pFAS, 6 Other								

## GRADE ratings for head circumference

		Certai	nty assessme	nt		Nº of pa	atients	Effe	ect	Certainty
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSU	RE STUDI	ES								
3irth Hea	ad Circum	nference <10 <sup>th</sup> P	ercentile							
ight pre	enatal alc	ohol exposure	(1-20g/w in a	t least one tri	mester)					
1	not serious	not serious	not serious	serious <sup>d</sup>	none	NR	NR <sup>g</sup>	<b>OR 0.99</b> (0.52 to 1.88)	1	⊕⊕⊕○ Moderate
Moderat	te prenat	al alcohol expo	sure (21-100g	/w in at least	t one tri	mester)				
1	not serious	not serious	not serious	serious <sup>d</sup>	none	NR	NR <sup>g</sup>	<b>OR 0.79</b> (0.19 to 3.29)	-	⊕⊕⊕○ Moderate
leavy pr	renatal al	cohol exposure	e (101-200g/w	in at least or	ne trime	ster) – no	studies			
Very hea	avy prena	tal alcohol exp	osure (201g+/	w in at least	one trin	nester)				
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	111	350	<b>OR 55.43</b> (3.15 to 975.09)	1	⊕⊕○○ Low
Any Leve	el, Confir	med-Level Unq	<b>uantifiable</b> – r	no studies						
3irth Hea	ad Circum	nference <3 <sup>rd</sup> Pe	ercentile							
Any Leve	el of Pren	atal Alcohol Ex	posure							
1	serious <sup>a</sup>	not serious	not serious	serious <sup>d,f</sup>	none	872	452	OR 0.71 (0.41 to 1.23)	-	⊕⊕○○ Low
ight, Mo	oderate,	Heavy, Very He	eavy, Confirme	ed-Unquantif	iable – r	o studies				
3irth Hea	ad Circum	nference Percer	ntile							
ight pre	enatal alc	ohol exposure	(1-20g/w in a	t least one tri	mester)					
1	seriousa	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	96	277	-	MD 0.70 lower (6.67 lower to 5.27 higher)	⊕○○○ Very Low
Moderat	te prenat	al alcohol expo	<u> </u>  sure (21-100g	/w in at least	t one tri	mester)			J.27 Higher	
-	serious	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	23	277	-	(13.91 lower to	⊕○○○ Very Low
			/404 200 /			. \			10.11 higher)	
	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	33	47	-	(3.87 lower to	⊕○○○ Very Low
Very hea	avy nrena	tal alcohol exp	 	w in at least	one trin	nester)			15.47 higher)	
	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>f</sup>	none	35	286	-	MD 11.97 lower (23.42 lower to 0.52 lower)	⊕○○○ Very Low
Any Leve	el, Confir	med-Unquantif	i <b>able</b> – no stu	dies						
		nference (cm)								
		ohol exposure	(1-20g/w in at	t least one tri	mester)					
1	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	112	97	-	MD 0.00 (0.35 lower to 0.35 higher)	⊕○○○ Very Low
Moderat	te prenat	al alcohol expo	sure (21-100g	/w in at least	t one tri	mester)				
	serious <sup>a</sup>	not serious	not serious	not serious	none	2188	144614	-	MD 0.19 lower (0.28 lower to 0.11 lower)	⊕⊕⊕○ Moderate
leavy pr	renatal al	cohol exposure	e (101-200g/w	in at least o	ne trime	ster)				

Very heavy prenatal alcohol exposure (201g+/w in at least one trimester)   2   Serious   Not serious   Not serious   Serious   Serious   Not serious   No	7	serious <sup>a</sup>	not serious	serious	not serious	none	295	1709	-	MD 0.78 lower (1.38 lower to	⊕⊕○○ Low
Any prenatal alcohol exposure (level dichotomised to yes/no)  1 serious not serious not serious serious serious none 28 28										0.19 lower)	
Any prenatal alcohol exposure (level dichotomised to yes/no)  1	Very he	avy prena	tal alcohol exp	osure (201g+/	w in at least	one trin	nester)				
Institute   Ins	2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	52	101	-	(2.81 lower to	⊕⊕○○ Low
Confirmed prenatal alcohol exposure-level unquantifiable (quasi heavy/very heavy)  3 serious' not serious not serious serious' none 146 93 - MD 0.85 lower 1.134 lower to 0.36 lower)  Postnatal Head Circumference (<10° percentile) Light prenatal alcohol exposure (1-20g/w in at least one trimester)  1 not not serious not serious serious' none NR NR* OR 0.81 (0.48 to 1.37) Moderate Moderate prenatal alcohol exposure (21-100g/w in at least one trimester)  2 not not serious none NR NR* OR 1.94 (1.04 to 1.37) Moderate Might Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)  1 serious' not serious not serious serious' 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' serious' serious' serious' serious' none 111 350 OR 4.34 (4.61 to 1817.39 Low Very heavy prenatal alcohol exposure (level dichotomised to yes/no) – no studies Confirmed prenatal alcohol exposure-level Unquantifiable  4 serious' not serious not serious serious' none 449 430 OR 1.05 (6.51 to 17.09)  Deportumental alcohol exposure (1-20g/w in at least one trimester)  1 serious' not serious serious' serious' none 112 97 - MD 2.00 lower (2.31 lower to 1.69 lower)  Moderate prenatal alcohol exposure (101-200g/w in at least one trimester)  2 serious' not serious serious' serious' none 110 111 - MD 1.42 lower to 0.68 lower)  Wery Low Oestnatal Head Circumference > 12months (cm)  Uight prenatal alcohol exposure (101-20g/w in at least one trimester)  1 serious' not serious serious' serious' none 110 111 - MD 1.42 lower to 0.68 lower)  1 serious' not serious serious' none exposure (2.1100g/w in at least one trimester)  1 serious' not serious serious' serious' none 22 21 - MD 0.48 lower to 0.28 lower to 0.29 lower to 0.29 lower to 0.29 lower to 0.	Any pre	natal alco	hol exposure (	evel dichoton	nised to yes/	no)					•
3   Serious   not serious   not serious   serious   serious   none   146   93   -     MD 0.85 lower   (1.34 lower to 0.36 lower)	1	serious <sup>a</sup>	not serious	- not serious	- serious <sup>d,f</sup>	none	28	28	-	(0.71 lower to	⊕⊕○○ Low
Postnatal Head Circumference (<10* percentile)  Light prenatal alcohol exposure (1-20g/w in at least one trimester)  1	Confirm	ed prena	tal alcohol expo	sure-level un	quantifiable	(quasi h	eavy/very	/ heavy)	_		
Light prenatal alcohol exposure (1-20g/w in at least one trimester)  1	3	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	146	93	-	(1.34 lower to	⊕⊕○○ Low
1 not serious not serious serious serious serious serious de none NR NR® NR® NR® NR® NR® NR® NR® NR® NR®	Postnat	al Head Ci	rcumference (<	10 <sup>th</sup> percentile	2)						
Serious   Seri	Light pr	enatal alc	ohol exposure	(1-20g/w in a	t least one tri	mester)					
2   not serious   not serious   not serious   not serious   none   NR   NR®h   OR 1.94 (1.04 to 3.62)   High		serious						NR <sup>g</sup>	,	-	⊕⊕⊕○ Moderate
Serious   Seri	Modera	te prenat	al alcohol expo	sure (21-100g	/w in at least	t one tri	mester)				
1 seriouss not serious not serious se		serious						NR <sup>g,h</sup>	,	-	⊕⊕⊕⊕ High
Very heavy prenatal alcohol exposure (201g+/w in at least one trimester)  2 seriouss serious seri	Heavy p	renatal a	cohol exposure	e (101-200g/w	ı	ne trime	•				
2 serious* serious* seriouse serious seriou	1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	14	26		-	⊕⊕○○ Low
Any prenatal alcohol exposure (level dichotomised to yes/no) – no studies  Confirmed prenatal alcohol exposure-Level Unquantifiable  4	Very he	avy prena	tal alcohol exp	osure (201g+/	w in at least	one trin	nester)				
Confirmed prenatal alcohol exposure-Level Unquantifiable  4    serious*   not serious   not serious   serious*   none   449   430   OR 10.55   (6.51 to 17.09)   -	2	serious <sup>a</sup>	serious⁵	serious	serious <sup>e,f</sup>	none	111	350		-	⊕○○○ Very Low
4 serious³ not serious not serious seriouse.f none 449 430 OR 10.55 (6.51 to 17.09)  Postnatal Head Circumference > 12months (cm)  Light prenatal alcohol exposure (1-20g/w in at least one trimester)  1 serious³ not serious serious serious seriousf none 112 97 - MD 2.00 lower (2.31 lower to 1.69 lower)  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 serious³ not serious serious serious seriousg.f none 110 111 - MD 1.42 lower (2.15 lower to 0.68 lower)  Very Heavy prenatal alcohol exposure (201g+/w in at least one trimester)  1 serious³ not serious not serious seriousg.f none 22 21 - MD 0.45 lower (1.28 lower to 0.38 higher)  Any prenatal alcohol exposure (level dichotomised to yes/no) - no studies  Confirmed prenatal alcohol exposure (level dichotomised to yes/no) - no studies  Confirmed prenatal alcohol exposure Level Unquantifiable  4 serious³ serious³ serious not serious serious seriousf none 86 121 - MD 1.21 lower (2.40 lower to 0.02 lower)  Very Low	Any pre	natal alco	hol exposure (	level dichoton	nised to yes/	<b>no)</b> – no	studies				
Postnatal Head Circumference > 12months (cm)  Light prenatal alcohol exposure (1-20g/w in at least one trimester)  1	Confirm	ed prena	tal alcohol expo	osure-Level Ui	nquantifiable						
Light prenatal alcohol exposure (1-20g/w in at least one trimester)  1	4	seriousª	not serious	not serious	serious <sup>e,f</sup>	none	449	430		-	
1 serious® not serious serious serious serious none 112 97 - MD 2.00 lower (2.31 lower to 1.69 lower)  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® not serious serious serious serious® none 110 111 - MD 1.42 lower (2.15 lower to 0.68 lower)  Very Heavy prenatal alcohol exposure (201g+/w in at least one trimester)  1 serious® not serious not serious serious serious serious serious serious not serious serious not serious serious none 22 21 - MD 0.45 lower (1.28 lower to 0.38 higher)  Any prenatal alcohol exposure (level dichotomised to yes/no) - no studies  Confirmed prenatal alcohol exposure-Level Unquantifiable  4 serious® serious® not serious serious serious serious serious serious not serious	Postnat	al Head Ci	rcumference >	12months (cm	1)			•	1		1
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	Light pr	enatal alc	ohol exposure	(1-20g/w in a	t least one tri	mester)					
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	1	serious <sup>a</sup>	not serious	serious	serious <sup>f</sup>	none	112	97	-	(2.31 lower to	⊕○○○ Very Low
Heavy prenatal alcohol exposure (101-200g/w in at least one trimester)  2	Modera	te prenat	al alcohol expo	sure (21-100g	/w in at least	t one tri	mester) –	no studie	es	2.03 10.0017	
2 serious   not serious		•					•				
Very Heavy prenatal alcohol exposure (201g+/w in at least one trimester)  1		1	•		T		•	111	-	(2.15 lower to	⊕○○○ Very Low
Any prenatal alcohol exposure (level dichotomised to yes/no) – no studies  Confirmed prenatal alcohol exposure-Level Unquantifiable  4 serious serious not serious serious not serious serious serious serious function not serious serious serious function not serious serio	Very He	avy prena	ital alcohol exp	osure (201g+,	/w in at least	one trin	nester)		•	•	
Any prenatal alcohol exposure (level dichotomised to yes/no) – no studies  Confirmed prenatal alcohol exposure-Level Unquantifiable  4    serious <sup>a</sup>   serious <sup>b</sup>   not serious   serious <sup>f</sup>   none   86    121    -   MD 1.21 lower (2.40 lower to 0.02 lower)   Very Low	1	serious <sup>a</sup>	not serious	not serious	serious <sup>d,f</sup>	none	22	21	-	(1.28 lower to	⊕⊕⊖⊖ Low
4 serious <sup>a</sup> serious <sup>b</sup> not serious serious <sup>f</sup> none 86 121 - MD 1.21 lower (2.40 lower to 0.02 lower)	Any pre	natal alco	hol exposure (	level dichoton	nised to yes/	<b>no)</b> – no	studies				
4 serious <sup>a</sup> serious <sup>b</sup> not serious serious <sup>f</sup> none 86 121 - MD 1.21 lower (2.40 lower to 0.02 lower)	Confirm	ed prena	tal alcohol expo	osure-Level Ui	nquantifiable						
			·	ı	•		86	121	-	(2.40 lower to	⊕○○○ Very Low
	Postnat	al Head Ci	rcumference Pe	ercentile							

		Very Heavy, Ar	•	•			dies			
leavy p	renatal al	cohol exposur	e (101-200g/v		ne trime	-				1
1	serious <sup>a</sup>	not serious	serious	serious <sup>d,f</sup>	none	30	44	-	MD 2.40 higher (13.82 lower to 18.62 higher)	⊕○○○ Very Low
DIAGNO	SED STU	DIES							, g	
Birth He	ad Circum	nference (cm)								
•	AS - NA									
FAS (p	FAS or pF	AS/FAS or dysr	norphic)	_			_			
3	serious <sup>a</sup>	serious⁵	serious∘	not serious	none	152	398	-	MD 1.07 lower (2.15 lower to 0)	⊕○○○ Very Low
Other (A	ARND, ND	-AE, SE-AE, No	n-syndromal)							
3	serious <sup>a</sup>	serious⁵	serious	not serious	none	214	398	-	MD 0.85 lower (1.65 lower to 0.05 lower)	⊕○○○ Very Low
ostnata	al Head Ci	rcumference (c	m) (6-9 yrs)							
ASD										
3	serious <sup>a</sup>	serious⁵	not serious	serious <sup>d,f</sup>	none	69	170	-	MD 0.59 lower (1.59 lower to 0.41 higher)	⊕○○○ Very Low
AS							_			
7	serious <sup>a</sup>	not serious	serious	not serious	none	383	956	-	MD 2.72 lower (2.94 lower to 2.50 lower)	⊕⊕○○ Low
FAS (p	FAS or pF	AS/FAS or dysr	norphic)							
6	serious <sup>a</sup>	serious⁵	serious	not serious	none	195	775	-	MD 1.86 lower (2.40 lower to 1.31 lower)	⊕○○○ Very Low
Other (A	ARND, ND	-AE, SE-AE, No	n-syndromal)							
3	serious	serious⁵	serious	seriousd	none	197	383	-	MD 0.81 lower (1.66 lower to 0.04 higher)	⊕○○○ Very Low
ostnata	al Head Ci	rcumference (c	ms) (9-18 yrs)							
ASD										
1	serious <sup>a</sup>	not serious	serious	serious <sup>e,f</sup>	none	13	12	1	MD 2.00 lower (3.70 lower to 0.30 lower)	⊕○○○ Very Low
AS										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	44	116	ı	MD 3.44 lower (4.22 lower to 2.67 lower)	⊕⊕⊖⊖ Low
FAS (p	FAS or pF	AS/FAS or dysr	norphic)							
2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	72	122	-	MD 1.33 lower (1.97 lower to 0.68 lower)	⊕⊕○○ Low
Other (A	ARND, ND	-AE, SE-AE, No	n-syndromal)							
4	serious <sup>a</sup>	serious⁵	serious	serious⁴	none	264	204	-	MD 0.49 lower (1.08 lower to 0.10 higher)	⊕○○○ Very Low
ostnata	al Head Ci	rcumference C	entiles							
ASD – ı	no studies									

FAS										
7	serious	serious⁵	not serious	not serious	none	200	2475	-	MD 48.17 lower (58.24 lower to 38.11 lower)	⊕⊕⊖⊖ Low
pFAS (p	FAS or pF	AS/FAS or dysi	morphic)							
9	serious <sup>a</sup>	serious⁵	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, No	n-syndromal)							
7	serious <sup>a</sup>	serious <sup>ь</sup>	not serious	serious <sup>d</sup>	none	209	2124	-	MD 11.32 lower (23.93 lower to 1.3 higher)	⊕○○○ Very Low
Postnat	tal Head Ci	rcumference <	3 <sup>rd</sup> Percentile							
FASD										
1	serious <sup>a</sup>	not serious	serious	serious <sup>d,f</sup>	none	26	27	<b>OR 0.69</b> (0.23 to 2.06)	-	⊕○○○ Very Low
FAS										
4	serious	serious⁵	not serious	serious <sup>e,f</sup>	none	119	1525	OR 43.15 (14.11 to 131.97)	-	⊕○○○ Very Low
pFAS (p	FAS or pF	AS/FAS or dysi	morphic)	•	•					•
5	serious <sup>a</sup>	serious⁵	not serious	very serious <sup>d,e,f</sup>	none	162	1541	OR 4.59 (1.16 to 18.13)	-	⊕○○○ Very Low
Other (	ARND, ND	-AE, SE-AE, No	n-syndromal)							
5	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	149	1541	OR 9.01 (4.06 to 20.04)	-	⊕⊕○○ Low
Postnat	tal Head Ci	rcumference <	10 <sup>th</sup> Percentile	!						
FASD										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	62	126	OR 24.18 (3.01 to 194.55)	-	⊕⊕○○ Low
FAS										
6	serious	serious⁵	not serious	serious <sup>e,f</sup>	none	239	1756	OR 63.26 (15.78 to 253.70)	-	⊕○○○ Very Low
pFAS (p	FAS or pF	AS/FAS or dysi	morphic)							
4	serious	serious⁵	not serious	serious <sup>e,f</sup>	none	142	1525	OR 3.65 (1.51 to 8.80)	-	⊕○○○ Very Low
Other (	ARND, ND	-AE, SE-AE, No	n-syndromal)							
5	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	242	1710	OR 4.23 (2.41 to 7.43)	-	⊕⊕○○ Low

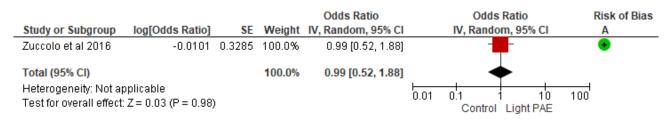
Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

**Explanations:** a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ( $1^2$  >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; f) 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

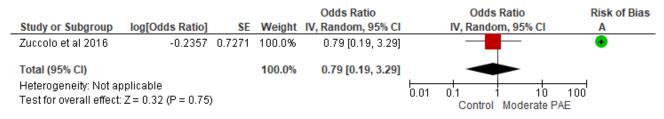
#### Head Circumference at Birth <10th Percentile

#### 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)



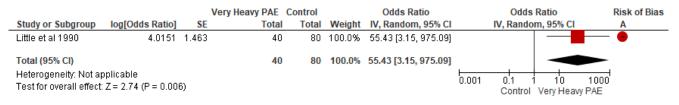
Risk of bias legend
(A) Overall risk of Bias

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

#### Heavy PAE and Head Circumference at Birth <10<sup>th</sup> Percentile (0 studies)

-

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



Risk of bias legend
(A) Overall risk of Bias

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

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

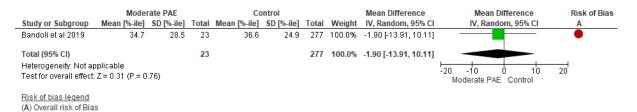
-

#### Head Circumference Percentile at Birth

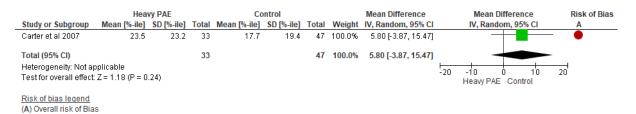
#### Light PAE and Head Circumference Percentile at Birth (1 study)



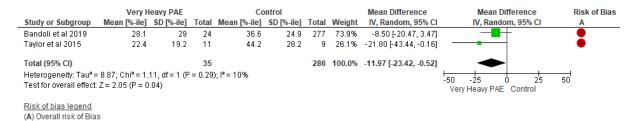
#### Moderate PAE and Head Circumference Percentile at Birth (1 study)



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



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



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)



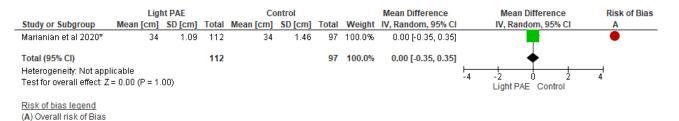
Risk of bias legend

(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)



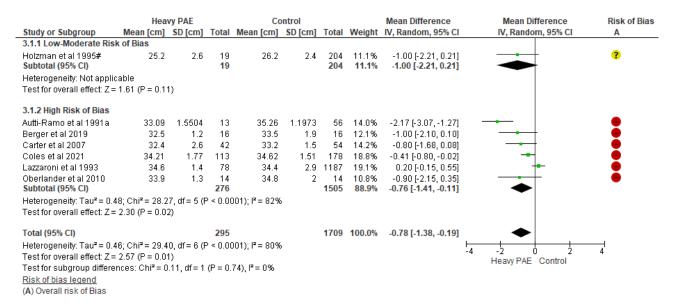
*Note:* Marianian et al 2020 = mean and SD estimated from median and interquartile range.

#### Moderate PAE and Head Circumference at Birth (4 studies)



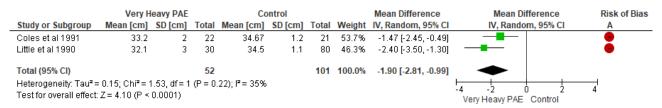
Note: #Holzman – sample were premature neonates

#### Heavy PAE and Head Circumference at Birth (7 studies)



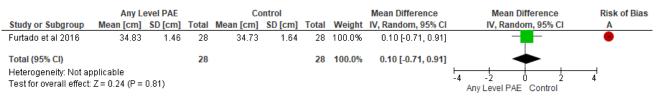
Note: #Holzman – sample were premature neonates.

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



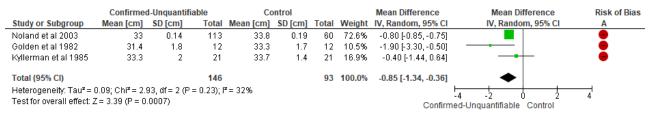
Risk of bias legend (A) Overall risk of Bias

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



Risk of bias legend
(A) Overall risk of Bias

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

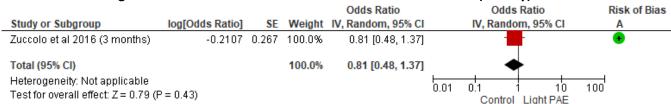


Risk of bias legend
(A) Overall risk of Bias

#### Postnatal head circumference

#### Postnatal Head Circumference <10th Percentile

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

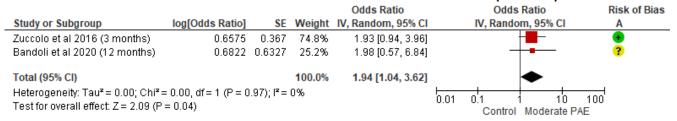


#### Risk of bias legend

(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 <10<sup>th</sup> Percentile (1 study)

			Heavy PAE C	ontrol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Korkham et al 1998 (5-9 yrs)	4.5168	1.5247	14	26	100.0%	91.54 [4.61, 1817.39]		<b>→</b> •
Total (95% CI)			14	26	100.0%	91.54 [4.61, 1817.39]	-	_
Heterogeneity: Not applicable Test for overall effect: Z = 2.96							0.001 0.1 1 10 1 Control Heav PAE	000

Risk of bias legend

(A) Overall risk of Bias

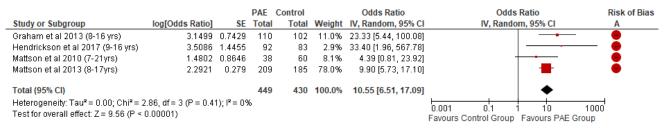
#### Very Heavy PAE and Postnatal Head Circumference <10<sup>th</sup> Percentile (2 studies)

		1	Very Heavy PAE	Control		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020 (12 months)	1.9695	0.5928	19	253	47.5%	7.17 [2.24, 22.91]		?
Kuehn et al 2012 (birth-8.5yrs)	1.0152	0.5538	92	97	52.5%	2.76 [0.93, 8.17]	<del></del>	?
Total (95% CI)			111	350	100.0%	4.34 [1.71, 11.06]	•	
Heterogeneity: Tau² = 0.13; Chi² =	1.38, $df = 1$ ( $P = 0$ .	.24); $I^2 = 2$	28%				0.01 0.1 1 10 100	
Test for overall effect: Z = 3.08 (P =	= 0.002)						Control Very Heavy PAE	

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)



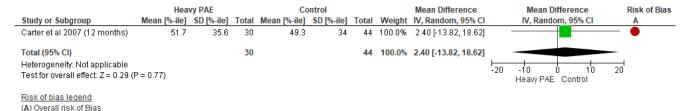
Risk of bias legend
(A) Overall risk of Bias

#### 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)

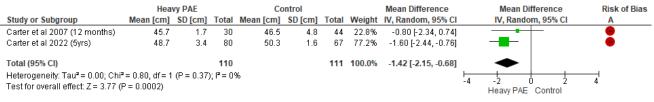
#### Light PAE and Postnatal Head Circumference (1 study)

	-	nt PAE			ontrol			Mean Difference	Me	an Difference	Risk of Bias
Study or Subgroup	Mean [cm]	SD [cm]	Total	Mean [cm]	SD [cm]	Total	Weight	IV, Random, 95% CI	IV, R	Random, 95% CI	Α
Marianian et al 2020*	34	1.09	112	34	1.46	97	100.0%	0.00 [-0.35, 0.35]			•
Total (95% CI)			112			97	100.0%	0.00 [-0.35, 0.35]		<b>+</b>	
Heterogeneity: Not app									-4 -7	<del>                                     </del>	<u> </u>
Test for overall effect: Z	= 0.00 (P = 1.	00)							Light	PAE Control	•
Risk of bias legend											

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

#### Moderate PAE and Postnatal Head Circumference (0 studies)

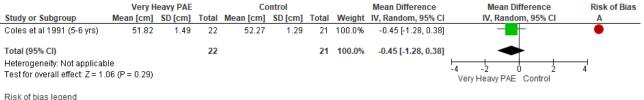
#### Heavy PAE and Postnatal Head Circumference (2 studies)



Risk of bias legend
(A) Overall risk of Bias

(A) Overall risk of Bias

#### Very Heavy PAE and Postnatal Head Circumference (1 study)



(A) Overall risk of Bias

Any Level PAE and Postnatal Head Circumference (0 studies)

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

	Confirmed	d-Unquantifia	ıble	Co	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [cm]	SD [cm]	Total	Mean [cm]	SD [cm]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chandran et al 2021 (9-10 yrs)	49.5	1.2	28	49.6	1.3	30	30.5%	-0.10 [-0.74, 0.54]	+	•
Golden et al 1982 (6-20 months)	41.8	2.8	12	45.9	1.9	12	17.9%	-4.10 [-6.01, -2.19]		•
Kyllerman et al 1985 (70-74 months)	50	2.9	21	51.3	1.9	21	22.0%	-1.30 [-2.78, 0.18]	<del></del>	
Roos et al 2021 (2-3 yrs)	49.26	1.67	25	49.8	1.28	58	29.7%	-0.54 [-1.27, 0.19]	-	•
Total (95% CI)			86			121	100.0%	-1.21 [-2.40, -0.02]	•	
Heterogeneity: Tau <sup>2</sup> = 1.10; Chi <sup>2</sup> = 16.0		).001); I² = 81	%						-10 -5 0 5	10
restror overall effect: Z = 2.00 (P = 0.05	Test for overall effect: Z = 2.00 (P = 0.05)							Confirm	ed-Unquantifiable Control	

Risk of bias legend
(A) Overall risk of Rias

#### **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)

	ľ									
	p	FAS		Co	ntrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [cm]	SD [cm]	Total	Mean [cm]	SD [cm]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Coles et al 2002 (dsymorphic)	33.42	1.7	46	33.53	1.76	53	35.5%	-0.11 [-0.79, 0.57]	<del></del>	•
Davies et al 2017 (FAS/pFAS)	32.2	2.7	25	34.8	1.9	32	26.6%	-2.60 [-3.85, -1.35]	<del></del>	•
Hasken et al 2021 (pFAS)	32.8	2	81	33.7	2.5	313	37.9%	-0.90 [-1.42, -0.38]		•
Total (95% CI)			152			398	100.0%	-1.07 [-2.15, 0.00]	•	
Heterogeneity: Tau² = 0.72; Chi² Test for overall effect: Z = 1.96 (F		2 (P = 0.00	2); l² =	83%					-4 -2 0 2 pFAS Control	4

Risk of bias legend
(A) Overall Risk of Bias Score

#### Other FASDs and Head Circumference at Birth (3 studies)

	ARN	D/Other		Co	ntrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [cm]	SD [cm]	Total	Mean [cm]	SD [cm]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Coles et al 2002 (Non-Syn)	33.38	2.53	82	33.53	1.76	53	32.8%	-0.15 [-0.87, 0.57]	<del></del>	
Davies et al 2017 (Non-Syn)	33.9	2.4	54	34.8	1.9	32	28.2%	-0.90 [-1.82, 0.02]	<del></del>	•
Hasken et al 2021 (ARND)	32.3	1.7	78	33.7	2.5	313	38.9%	-1.40 [-1.87, -0.93]	-	•
Total (95% CI)			214			398	100.0%	-0.85 [-1.65, -0.05]	•	
Heterogeneity: Tau² = 0.37; Ch Test for overall effect: Z = 2.07	•	2 (P = 0.0)	2); l² = 1	75%					-4 -2 0 2 4 ARND/Other Control	J

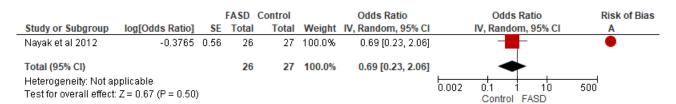
Risk of bias legend

(A) Overall Risk of Bias Score

#### Postnatal head circumference

#### Postnatal Head Circumference <3rd Percentile

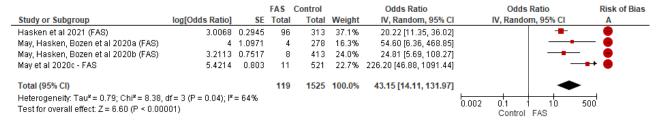
#### FASD and Postnatal Head Circumference <3<sup>rd</sup> Percentile (1 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

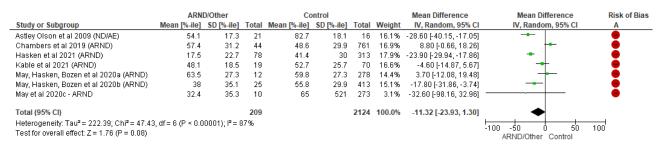
#### FAS and Postnatal Head Circumference <3<sup>rd</sup> Percentile (4 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

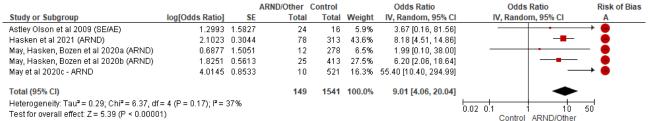
#### pFAS and Postnatal Head Circumference <3<sup>--</sup> Percentile (5 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

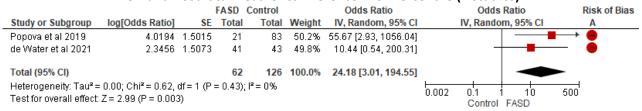
#### Other FASDs and Postnatal Head Circumference 3rd Percentile (5 studies)



Risk of bias legend
(A) Overall Risk of Bias Score

#### Postnatal Head Circumference <10th Percentile

#### FASD and Postnatal Head Circumference <10<sup>th</sup> Percentile (2 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

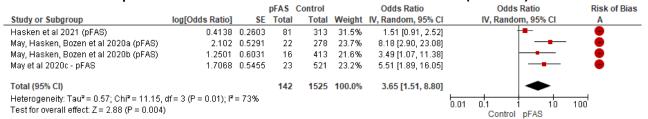
#### FAS and Postnatal Head Circumference <10th Percentile (6 studies)

			FAS	Control		Odds Ratio	C	odds Ratio	Risk of Bias
Study or Subgroup	log[Odds Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Ra	andom, 95% CI	Α
Hasken et al 2021 (FAS)	1.9904	0.2666	96	313	25.7%	7.32 [4.34, 12.34]		-	•
Mattson et al 2010 (FAS)	5.9041	1.4728	41	46	12.4%	366.54 [20.44, 6573.06]			<del></del> → 🛑
Mattson et al 2013 (FAS)	3.5768	0.3765	79	185	24.8%	35.76 [17.10, 74.79]		-	•
May, Hasken, Bozen et al 2020a (FAS)	5.0304	1.5135	4	278	12.0%	152.99 [7.88, 2971.45]			<b>→ ●</b>
May, Hasken, Bozen et al 2020b (FAS)	5.1695	1.4655	8	413	12.5%	175.83 [9.95, 3108.29]			<b>-</b> → ●
May et al 2020c - FAS	6.1044	1.4588	11	521	12.5%	447.82 [25.67, 7813.40]		_	<del></del> → ●
Total (95% CI)			239	1756	100.0%	63.26 [15.78, 253.70]		•	-
Heterogeneity: Tau² = 1.88; Chi² = 27.81	, df= 5 (P < 0.0001	); I <sup>2</sup> = 82 <sup>4</sup>	%				0.001 0.1	1 10	1000
Test for overall effect: Z = 5.85 (P < 0.00)	001)							ntrol FAS	1000

Risk of bias legend

(A) Overall Risk of Bias Score

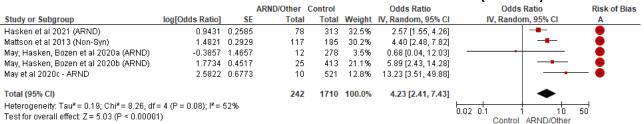
#### pFAS and Postnatal Head Circumference <10th Percentile (4 studies)



Risk of bias legend

(A) Overall Risk of Bias Score

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



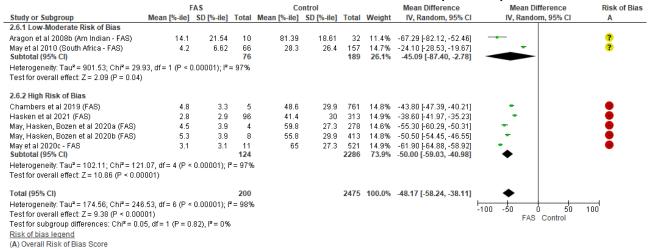
Risk of bias legend

(A) Overall Risk of Bias Score

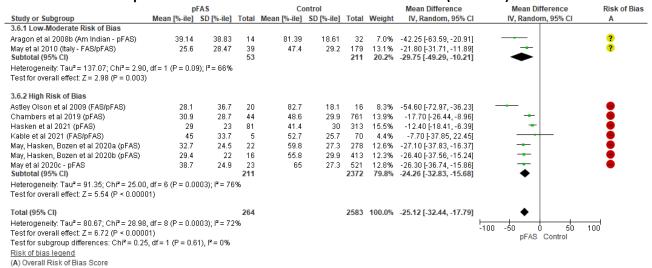
#### Postnatal Head Circumference Percentile

#### FASD and Postnatal Head Circumference Percentile (0 studies)

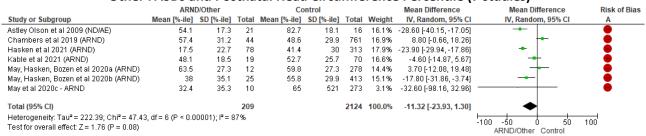
#### FAS and Postnatal Head Circumference Percentile (7 studies)



#### pFAS and Postnatal Head Circumference Percentile (9 studies)



#### Other FASDs and Postnatal Head Circumference Percentile (7 studies)

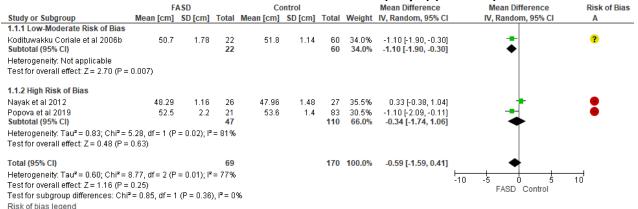


Risk of bias legend
(A) Overall Risk of Bias Score

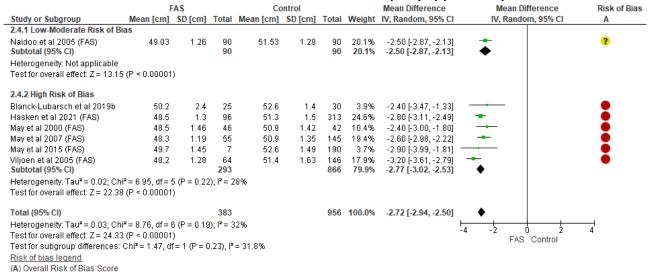
(A) Overall Risk of Bias Score

#### Postnatal Head Circumference (6-9 years)

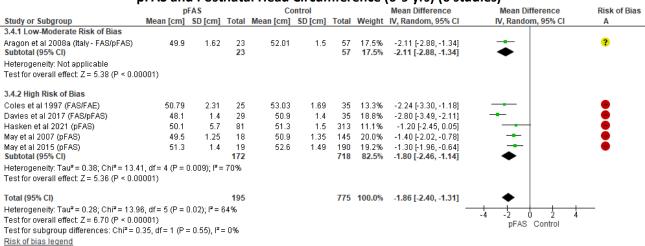
#### FASD and Postnatal Head Circumference (6-9yrs) (3 studies)



#### 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)

	ARN	D/Other		Control				Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [cm]	SD [cm]	Total	Mean [cm]	SD [cm]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Coles et al 1997 (Non-Syn)	52.91	1.55	62	53.03	1.69	35	31.5%	-0.12 [-0.80, 0.56]	+	•
Davies et al 2017 (Non-Syn)	44.5	1.8	57	45.2	1.4	35	31.9%	-0.70 [-1.36, -0.04]	-	•
Hasken et al 2021 (ARND)	49.8	1.5	78	51.3	1.5	313	36.6%	-1.50 [-1.87, -1.13]	•	•
Total (95% CI)			197			383	100.0%	-0.81 [-1.66, 0.04]	•	
Heterogeneity: Tau² = 0.48; Cl Test for overall effect: Z = 1.86		= 2 (P = 0.	0010);	l² = 86%					-10 -5 0 5 ARND/Other Control	10

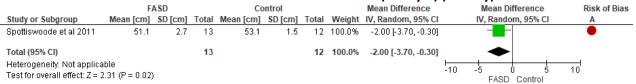
Risk of bias legend

(A) Overall Risk of Bias Score

(A) Overall Risk of Bias Score

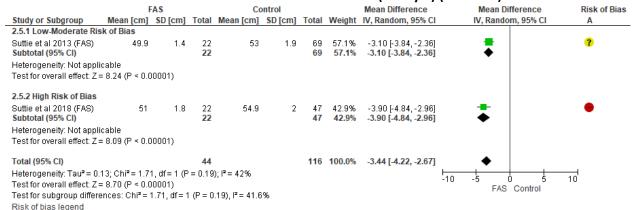
#### Postnatal Head Circumference (9-18 years)

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



Risk of bias legend
(A) Overall Risk of Bias Score

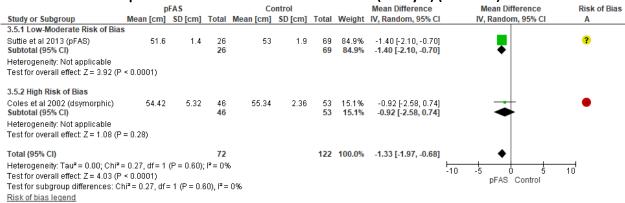
#### FAS and Postnatal Head Circumference (9-18 yrs) (2 studies)



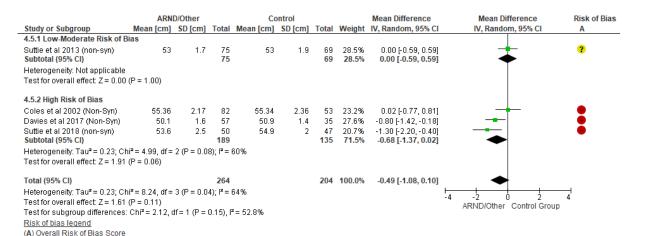
pFAS and Postnatal Head Circumference (9-18 yrs) (2 studies)

(A) Overall Risk of Bias Score

(A) Overall Risk of Bias Score



#### 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 Frequency of agenesis/hypogenesis of corpus	2 studies: FAS/pFAS (dysmorphic) and ARND/Others (non-dysmorphic) 2 studies: FAS/pFAS							
	callosum								

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

		Cert	ainty assessmer	nt		Nº of	patients	Eff	ect	Certainty
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSUR	EXPOSURE STUDIES									
Frequenc	y of clinical	ly significant incid	lental findings							
Confirme	d unquant	ified								
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	164	163	OR 2.53 (0.48 to 13.24)	-	⊕○○○ Very Low
DIAGNOS	ED STUDIE	S								
Frequenc	y of clinical	ly significant incic	lental findings							
FAS/pFAS	dysmorp	hic groups)								
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	6/57	2/179	OR 6.97 (1.46 to 33.34)	-	⊕⊕○○ Low
ARND/Ot	hers (non-	dysmorphic group	os)		•	1	•	·	•	
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	3/118	2/179	OR 1.36 (0.09 to 20.24)	-	⊕○○○ Very Low
Frequenc	y of agenes	sis/hypogenesis o	f the corpus call	osum						
FAS/pFAS	6									
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	4/33	0/28	OR 4.92 (0.54 to 44.79)	-	⊕○○○ Very Low

 $\textbf{Notes: CI:} confidence interval; \textbf{MD:} mean difference; \textbf{OR:} odds \ ratio.$ 

**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; f) 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)

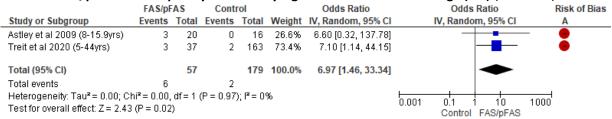


Risk of bias legend
(A) Overall RoB

#### **Diagnosed Studies**

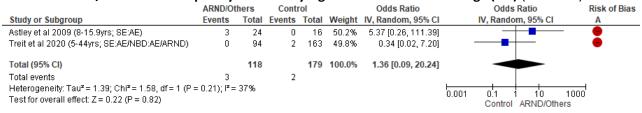
#### Frequency of clinically significant incidental findings (OR)

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



Risk of bias legend
(A) Overall RoB

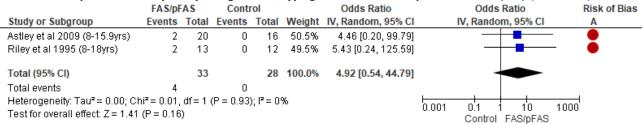
#### ARND/Others and frequency of clinically significant incidental findings (OR) (2 studies)



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	Total Intracranial volume, total brain	<b>8 PAE studies:</b> 1x light PAE, 1x moderate PAE, 2x					
studies	volume (cm³)	very heavy PAE, 3x confirmed unquantifiable					
	Left hippocampus (mm³)	<b>2x PAE studies:</b> 2x confirmed unquantifiable					
	Right Hippocampus (mm³)	1x PAE studies: 1x confirmed unquantifiable					
	Grey matter volume (cm³)	<b>2x PAE studies:</b> 1x very heavy PAE, 1x confirmed unquantifiable					
	Right putamen volume (mm/cm³)	2x PAE studies: 2x confirmed unquantifiable					
	Left putamen volume (mm/cm³)	2x PAE studies: 2x confirmed unquantifiable					
	Left amygdala (mm³)	2x PAE studies: 2x confirmed unquantifiable					
	Right amygdala (mm³)	2x PAE studies: 2x confirmed unquantifiable					
	Left thalamus (mm³)	2x PAE studies: 2x confirmed unquantifiable					
	Right thalamus (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Left Caudate (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Right Caudate (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Left Pallidum (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Right Pallidum (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Left Nucleus Accumens (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Right Nucelus Accumens (mm³)	1x PAE study: 1x confirmed unquantifiable					
	White matter volume (cm³)	2x PAE studies: 2x very heavy PAE					
	Total cortical brain volume (cm³)	2x PAE studies: 1x light PAE, 1x confirmed					
		unquantifiable					
	Left Caudate (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Right Caudate (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Left Hemisphere Volume (mm³)	1x PAE study: 1x confirmed unquantifiable					
	Right Hemisphere Volume (mm³)	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 (cm³)	1x PAE study: 1x confirmed unquantifiable					
	Left middle frontal (caudal) gyrus (cm³)	1x PAE study: 1x confirmed unquantifiable					
	Left paracentral gyrus (cm³)	1x PAE study: 1x confirmed unquantifiable					
	Left precentral gyrus (cm³)	1x PAE study: 1x confirmed unquantifiable					
	Left precuneus (cm³)	1x PAE study: 1x confirmed unquantifiable					
	Right precuneus (cm³)	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					

T	T
Anterior subdivision cingulate white matter (cc)	1x PAE study: 1x confirmed unquantifiable
Posterior subdivision cingulate white	1x PAE study: 1x confirmed unquantifiable
matter (cc)	TATAL Study. IX committee unquantimusic
Anterior vermis (I-V) area (mm³)	1x PAE study: 1x confirmed unquantifiable
Superior posterior vermis (VI-VII) area	1x PAE study: 1x confirmed unquantifiable
(mm³)	
Inferior posterior vermis (VIII-X) area	1x PAE study: 1x confirmed unquantifiable
(mm³)	
Corpus callosum and corona radiata (CCCR) (FA)	1x PAE study: 1x very heavy PAE
Left hemispheric projection fibres (L-PROJ)	1x PAE study: 1x very heavy PAE
(FA)	
Right hemispheric projection fibres (R-	1x PAE study: 1x very heavy PAE
PROJ) (FA)	
Left hemispheric association fibres (L-	1x PAE study: 1x very heavy PAE
ASSOC) (FA)	TATAL Study. IA VETY HEAVY FAL
Right hemispheric association fibres (R-	1x PAE study: 1x very heavy PAE
ASSOC) (FA)	IX FAL Study. IX VETY HEAVY FAL
Left paracentral lobule (FA)	1x PAE study: 1x light PAE
Left middle cingulate area (FA)	1x PAE study: 1x light PAE  1x PAE study: 1x light PAE
Left middle frontal area (FA)	
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 planun 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	10x studies: 6x FASD, 4x FAS/pFAS, 2x
(cm <sup>3</sup> )	ARND/Others
Right hippocampal volume (mm³)	<b>6x studies:</b> 3x FASD, 3x FAS/pFAS, 3x
	ARND/Others
Left hippocampal volume (mm³)	<b>6x studies:</b> 4x FASD, 2x FAS/pFAS, 3x
	ARND/Others
	/ iiii j o tiici j

Diagnosed	Total hippocampal volume (cm³)	<b>5x studies:</b> 2x FASD, 1x FAS/pFAS, 3x ARND/Others					
studies	Right caudate volume (mm³)	<b>5x studies:</b> 1x FASD, 4x FAS/pFAS, 2x ARND/Others					
	Left caudate volume (mm³)	<b>5x studies:</b> 1x FASD, 4x FAS/pFAS, 2x ARND/Others					
	Total caudate volume (cm³)	3x studies: 1x FASD, 1x FAS					
	Total putamen volume (cm³)	<b>3x studies:</b> 2x FASD, 1x FAS/pFAS, 1x ARND/Others					
	Right putamen volume (cm³)	<b>3x studies:</b> 2x FASD, 1x FAS/pFAS, 1x ARND/Others					
	Left putamen volume (cm³)	<b>3x studies:</b> 2x FASD, 1x FAS/pFAS, 1x ARND/Others					
	Corpus callosum volume (mm³)	2x studies: 2x FAS/pFAS, 1x ARND/Others					
	Total grey matter volume (cm <sup>3</sup> )	4x studies: 3x FASD, 1xFAS/pFAS					
	Cortical grey matter volume (cm <sup>3)</sup>	2x studies: 2x FASD					
	Total Subcortical grey matter (cm <sup>3</sup> )	4x studies: 4x FASD					
	Total white matter volume (cm <sup>3</sup> )	4x studies: 3x FASD, 1x FAS, 1x ARND/Others					
	Grey & white tissue volume (cm³)	1x study: 1x FASD					
	Frontal lobe volume (cm³)	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)	<b>3 studies:</b> 2x FASD, 1x FAS, 1x ARND/Others					
	Posterior midbody corpus callosum (FA)	<b>3 studies:</b> 2x FASD, 1x FAS, 1x ARND/Others					
	Isthmus corpus callosum (FA)	<b>4x studies:</b> 2x FASD, 2x FAS/pFAS, 2x ARND/Others					
	Splenium corpus callosum (FA)	<b>5x studies:</b> 3x FASD, 2x FAS/pFAS, 2x ARND/Others					
	Fusiform gyrus (mm³)	2x studies: 1x FASD, 1x ARND/Others					
	Cerebellar grey matter (cm³)	<b>3 studies:</b> 1x FASD, 2x FAS/pFAS, 2x ARND/Others					
	Cerebellar white matter (cm³)	<b>3 studies:</b> 1x FASD, 2x FAS/pFAS, 2x ARND/Others					
	Cerebellar volume (cm³)	2 studies: 1x FASD, 1x FAS, 1x ARND/Others					
	Medial orbital frontal (mm³)	2 studies: 1x FASD, 1x ARND/Others					
	Total cranial volume (cm³)	1x study: 1x FAS					
	Hippocampus	1x study: 1x FASD					
	Left amygdala (cm³)	2 studies: 2x FASD					
	Right amygdala (cm³)	2 studies: 2x FASD					
	Left thalamus (cm³)						
	· · ·	2 studies: 2x FASD					
	Right thalamus (cm³)	2 studies: 2x FASD					
	Thalamus (cm³)	2 studies: 2x FASD					
	Amygdala (cm³)	2 studies: 2x FASD					
	Frontal lobe grey matter volume (cm <sup>3</sup> )	1 study: 1x FAS/pFAS, 1x ARND/Others					
	Frontal lobe white matter volume (cm <sup>3)</sup>	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 <sup>3</sup> )	1x study: 1x ARND/Others					
	Lateral OFC (mm <sup>3</sup> )	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 (mm³)	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 <sup>3</sup> )	1x study: 1x FAS/pFAS, 1x ARND/Others					

1 (i Cl 1   D II: 1   / 2)	4
Left Globus Pallidus (cm³)	1x study: 1x FASD
Globus Pallidus (cm³)	1x study: 1x FASD
Right Globus Pallidus (cm³)	1x study: 1x FASD
Right anterior hippocampal volume (mm³)	1x study: 1x ARND/Others
Right posterior hippocampal volume (mm³)	1x study: 1x ARND/Others
Left anterior hippocampal volume (mm³)	1x study: 1x ARND/Others
Left posterior hippocampal volume (mm³)	1x study: 1x ARND/Others  1x study: 1x ARND/Others
Parahippocampal gyrus (mm³)	1x study: 1x ARND/Others  1x study: 1x ARND/Others
Entorhinal (mm³)	1x study: 1x ARND/Others  1x study: 1x ARND/Others
Parasubiculum	1x study: 1x AKNO/Others  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  1x study: 1x FASD
Tail	1x study: 1x FASD
Caudal middle frontal gyrus (mm³)	1x study: 1x ARND/Others
Superior frontal (mm³)	1x study: 1x ARND/Others
Rostral medial frontal (mm³)	1x study: 1x ARND/Others
Pars opercularis (mm³)	1x study: 1x ARND/Others
Pars triangularis (mm³)	1x study: 1x ARND/Others
Pars orbitalis (mm³)	1x study: 1x ARND/Others
Left nucleus accumbens (mm³)	1x study: 1x FAS/pFAS, 1x ARND/Others
Right nucleus accumbens (mm³)	1x study: 1x FAS/pFAS, 1x ARND/Others
PCC (mm³)	1x study: 1x FASD
Precuneus (mm³)	1x study: 1x FASD
STG (mm³)	1x study: 1x FASD
CC – Splenium area (mm³)	1x study: 1x ARND/Others
CC – Isthmus area (mm³)	1x study: 1x ARND/Others
CC – Posterior midbody area (mm³)	1x study: 1x ARND/Others
CC – Anterior midbody (mm³)	1x study: 1x ARND/Others
CC – Genu area (mm³)	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 splenuim (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 (cm³)	1x study: 1x FASD

1x study: 1x FASD
1x study: 1x FASD
1x study: 1x FAS/pFAS
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						patients	Effec	t	Certainty
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSU	EXPOSURE STUDIES									
Total Bra	Total Brain/Intracranial volume (cm³) (m/SD)									
Very hea	avy PAE									
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	22	18	SMD 0.22 lower (1.03 lower to 0.60 higher)	-	⊕⊕⊖⊖ Low
Confirm	ed Unquan	tifiable								
3	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	140	152	SMD 0.27 lower (0.50 lower to 0.04 lower)	-	⊕⊕⊖⊖ Low
White m	atter volun	ne (cm³) (m/SD)								
Very hea	avy PAE									
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	none	22	18	SMD 0.12 lower (1.24 lower to 0.99 higher)	-	⊕○○○ Very Low
Left Hipp	ocampus (	mm³) (m/SD)								
Confirme	ed Unquant	tifiable								
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	48	93	SMD 0.43 lower (0.78	-	⊕⊕○○ Low

			<u> </u>	ı				T		
								lower to 0.08 lower)		
Right Pu	tamen (mm	n <sup>3</sup> or cm <sup>3</sup> ) (m/SD	<u> </u>	<u> </u>				0.08 lower)		
	ed Unquant		,							
	•			1		67	160	CN4D 0 2C		2000
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	67	168	SMD 0.26 lower (0.73	-	ФООО
				Serious				lower to		Very Low
								0.20 higher)		
Left Puta	amen (mm³	or cm <sup>3</sup> ) (m/SD)						0.20 mgner/		
	ed Unquant									
2	serious	not serious	not serious	serious <sup>e,f</sup>	none	67	168	SMD 0.43	_	0000
	serious	not serious	not serious	Serious	Hone	07	100	lower (0.86	-	⊕⊕○○ Low
								lower to		LOW
								0.00 lower)		
Left Amy	ygdala (mm	<sup>3</sup> ) (m/SD)	L	L				,		
	ed Unquant									
2	seriousa	not serious	not serious	very	none	48	89	SMD 0.30	_	ФООО
_	Scrious	1100 3011003	not serious	serious <sup>d,e,f</sup>	110110	10	03	lower (0.65		Very Low
								lower to		Very Low
								0.06 higher)		
Right An	nygdala (mr	n³) (m/SD)								
Confirme	ed Unquant	ifiable								
2	seriousa	not serious	not serious	very	none	48	89	SMD 0.13	_	ФООО
_				serious <sup>d,e,f</sup>				lower (0.48		Very Low
								lower to		,
								0.23 higher)		
Left Tha	lamus (mm	<sup>3</sup> ) (m/SD)								
Confirme	ed Unquant	ifiable								
2	seriousa	not serious	not serious	very	none	48	89	SMD 0.27	-	ФООО
				serious <sup>d,e,f</sup>				lower (0.63		Very Low
								lower to		
								0.08 higher)		
	SED STUD									
Total bra	ain/intracra	nial volume (cm	³) (m/SD)							
FASD										
6	seriousa	not serious	not serious	not serious	none	277	275	SMD 0.61	-	$\Theta\Theta\Theta\Theta$
								lower (0.78		Moderate
								lower to		
_								0.44 lower)		
FAS/pFA			T	1						1
4	seriousa	not serious	not serious	serious <sup>e,f</sup>	none	114	116	SMD 0.87	-	$\Theta\Theta\bigcirc\bigcirc$
								lower (1.29		Low
								lower to		
ARND/O	    there							0.44 lower)		
				a a mi a d a f		4.0	25	CNAD O 30		0000
2	serious <sup>a</sup>	not serious	not serious	serious <sup>d,e,f</sup>	none	46	35	SMD 0.28 lower (0.79	-	<b>ӨӨОО</b>
								lower to		Low
								0.23 higher)		
Right hir	pocampal	volume (mm³) (r	n/SD)	<u> </u>				5.25 mgner/		
FASD		- ( / (.	. ,							
3	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	125	153	_	SMD 0.56	_	$\Phi \cap \cap \cap$
] 3	serious	serious"	HOL SELIOUS	serious"	123	102	-	lower (1.04	-	#000
	]		<u>I</u>	<u> </u>				.5.35. (2.07		Very Low

			1		ı	1		1 .		
								lower to		
EAC/EA								0.08 lower)		
FAS/pFA			1	-	1	_		1		<b>,</b>
3	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	57	36	-	SMD 0.64	-	ФООО
								lower (1.15		Very Low
								lower to		
								0.13 lower)		
ARND/O	thers									
3	seriousa	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	70	36	-	SMD 0.60	-	$\oplus$
								lower (0.96		Very Low
								lower to		
								0.25 lower)		
Left hipp	ocampal vo	olume (mm³) (m	/SD)							
FASD										
4	seriousa	not serious	not serious	serious <sup>e,f</sup>	134	172	-	SMD 0.60	-	<b>0000</b>
								lower (0.96		Low
								lower to		
								0.25 lower)		
FAS/pFA	S									
2	seriousa	not serious	not serious	serious <sup>e,f</sup>	48	17	-	SMD 0.83	-	<b>ФФ</b> ОО
=								lower (1.49		Low
								lower to		20
								0.18 lower)		
ARND/O	thers							,		•
2	seriousa	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	70	36	_	SMD 0.70	_	ФООО
-	3011003	not serious	Scrious	3611043	, ,			lower (1.15		Very Low
								lower to		Very Low
								0.26 lower)		
Total hip	pocampal v	olume (mm³) (r	n/SD)		ı					
FASD		. , , , ,	· ·							
				a a wi a v a f	120	144		CNAD O CO		
2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	139	144	-	SMD 0.69 lower (0.93	-	⊕⊕○○
								lower to		Low
								0.45 lower)		
ARND/O	thors					<u> </u>		0.43 lower)		L
		· h			l =0	T = 0				
3	serious <sup>a</sup>	serious <sup>b</sup>	not serious	very	78	59	-	SMD 1.30	=	ФООО
				serious <sup>d,e,f</sup>				lower (2.62		Very Low
								lower to		
Dight car	idata valua	ne (mm³) (m/SD	\					0.03 higher)		L
		ie (iiiiii°) (m/SD	J							
FAS/pFA										
4	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	81	83	-	SMD 1.49	-	$\Theta$
								lower (2.45		Very Low
								lower to		
								0.52 lower)		
ARND/O	thers									
2	seriousa	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	48	17	-	SMD 1.05	-	ФООО
								lower (1.70		Very Low
								lower to		
								0.40 lower)		
Left caud	date volume	e (mm³) (m/SD)								
FAS/pFA	S									
4	seriousa	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	54	110	_	SMD 1.03	_	ФООО
7	Jerious	3011003	not senous	SCITIOUS ?	)-	110	_	lower (1.84	-	Very Low
					<u> </u>	<u> </u>		.0 (1.07		VEIY LOW

								lower to		
								0.21 lower)		
ARND/C	Others							0.21.000.017		
2	seriousa	not serious	not serious	serious <sup>e,f</sup>	48	17	_	SMD 1.02	_	<b>ФФ</b> ОО
-	3011003	1100 3011003	not serious	3011003	40	1 -/		lower (1.66		Low
								lower to		LOW
								0.37 lower)		
Total ca	udate volun	ne (mm³) (m/SD	)							
FASD										
2	seriousa	not serious	not serious	serious <sup>e,f</sup>	139	144	-	SMD 0.88	-	$\Theta\Theta\bigcirc\bigcirc$
								lower (1.13		Low
								lower to		
	<u> </u>	/ 2) / /05						0.64 lower)		
FASD	itamen volu	me (mm³) (m/S[	))							
				i f	100	125		CN4D 0 C4		
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	106	135	-	SMD 0.64	-	##OO
								lower (1.00 lower to		Low
								0.28 lower)		
Right nu	ıtamen volu	me (mm³) (m/SI	) )					0.20 lowery		
FASD		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	- /							
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	106	135	_	SMD 0.96	_	⊕○○○
_	30.7000	50.100.5		551.54.5				lower (1.78		Very Low
								lower to		,
								0.14 lower)		
Left puta	amen volum	ne (mm³) (m/SD)								
FASD										
2	seriousa	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	106	135	-	SMD 0.79	-	ФООО
								lower (1.29		Very Low
								lower to		
		1 / 2) / /	(D)					0.29 lower)		
-		lume (mm³) (m/	(טא							
FAS/pFA				i f	F0	1 40		CN4D 4 20		
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	50	48	-	SMD 1.29	-	<b>⊕⊕</b> ○○
								lower (1.83 lower to		Low
								0.76 lower)		
Total gre	ey matter vo	olume (cm³) (m/	SD)					0.75 lower/		
FASD		, , ,								
3	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	175	205	-	SMD 0.67	-	<b>@@O</b> O
								lower (0.88		Low
								lower to		
								0.46 lower)		
	grey matter	volume (cm³) (	m/SD)							
FASD										
2	seriousa	not serious	not serious	serious <sup>e,f</sup>	78	87	-	SMD 0.68	-	$\oplus \oplus \bigcirc \bigcirc$
								lower (0.99		Low
								lower to		
Total cu	heartical are	ey matter volum	e (cm3) (m/sp)					0.36 lower)		
FASD	beortical gre	ey matter volum	e (ciii-) (iii/3D)							
4 4	seriousª	not serious	not serious	not serious	183	218	_	SMD 0.90	_	ΦΦΦ
-	3erious	1101 3511003	not serious	1101 3511003	103	210	_	lower (1.13	-	⊕⊕⊕○ Moderate
<u> </u>	I		<u> </u>	<u> </u>	l	1		(1.15		iviouerate

			I					lower to		
								0.66 lower)		
Total wh	nite matter v	olume (cm³) (m	n/SD)							
FASD										
4	serious <sup>a</sup>	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	176	167	-	SMD 0.04 lower (0.65 lower to 0.57 higher)	-	⊕○○○ Very Low
Genu co	rpus callosu	ım (FA) (m/SD)						o.or mgnery		
FASD	•	. , , , ,								
3	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	146	128	-	SMD 0.42 lower (0.66 lower to 0.17 lower)	-	⊕⊕○○ Low
Rostral I	Body Corpus	Callosum (FA)	(m/SD)							
FASD										
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	76	54	-	SMD 0.02 lower (0.37 lower to 0.33 higher)	-	⊕○○○ Very Low
Anterior	Midbody C	orpus Callosum	(FA) (m/SD)							
FASD										
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	76	54	-	SMD 0.00 (0.35 lower to 0.35 higher)	-	⊕○○○ Very Low
Posterio	r midbody o	corpus callosum	(FA) (m/SD)							•
FASD										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	76	54	-	SMD 0.44 lower (0.80 lower to 0.09 lower)	-	⊕⊕○○ Low
Isthmus	corpus callo	osum (FA) (m/SI	0)							
FASD										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	76	54	-	SMD 0.45 lower (0.81 lower to 0.09 lower)	-	⊕⊕○○ Low
FAS/pFA	AS									
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	54	38	-	SMD 1.05 lower (1.76 lower to 0.34 lower)	-	⊕⊕○○ Low
Spleniur	m corpus cal	losum (FA) (m/s	SD)					,		•
FASD										
3	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	146	128	-	SMD 0.18 lower (0.58 lower to 0.21 higher)	-	⊕○○○ Very Low
FAS/pF/	AS		1					5,		
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	54	38	-	SMD 0.91 lower (1.74 lower to 0.07 lower)	-	⊕○○○ Very Low

ARND/C	Others									
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	44	38	-	SMD 0.36 lower (0.80 lower to 0.08 higher)	-	⊕○○○ Very Low
Cerebel	lar grey mat	ter (cm³) (m/SD	)							
FAS/pF	AS									
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	80	67	-	SMD 1.12 lower (2.18 lower to 0.06 lower)	-	⊕⊕○○ Low
ARND/C				<b>.</b>						·
2	serious <sup>a</sup>	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	74	67	-	SMD 0.40 lower (1.81 lower to 1.00 higher)	-	⊕○○○ Very Low
Cerebel	lar white ma	atter (cm³) (m/S	D)							
FAS/pFA	AS									
2	seriousa	not serious	not serious	serious <sup>e,f</sup>	80	67	1	SMD 1.19 lower (1.58 lower to 0.79 lower)	•	⊕⊕○○ Low
ARND/C	Others			_						_
2	seriousa	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	74	67	1	SMD 0.65 lower (2.07 lower to 0.76 higher)	•	⊕○○○ Very Low
Left amy	ygdala (cm³)	(m/SD)								
FASD										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	106	135	-	SMD 0.57 lower (0.83 lower to 0.31 lower)	-	⊕⊕○○ Low
Right an	nygdala (cm	<sup>3</sup> ) (m/SD)						,		
FASD										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	106	135	-	SMD 0.50 lower (0.76 lower to 0.24 lower)	-	⊕⊕⊖⊖ Low
	lamus (cm³)	(m/SD)								
FASD										
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	106	135	-	SMD 0.83 lower (1.37 lower to 0.29 lower)	-	⊕○○○ Very Low
	alamus (cm <sup>3</sup>	<sup>3</sup> ) (m/SD)								
FASD										
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	106	135	-	SMD 0.86 lower (1.44 lower to 0.27 lower)	1	⊕○○○ Very Low
Thalamı	us (cm³) (m/	SD)								
FASD										

2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	139	144	-	SMD 0.70 lower (0.94 lower to 0.46 lower)	-	⊕⊕○○ Low
Amygdal	la (cm³) (m/	/SD)								
FASD										
2	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	139	144	-	SMD 0.25 lower (0.48 lower to 0.01 lower)	-	⊕⊕○○ Low

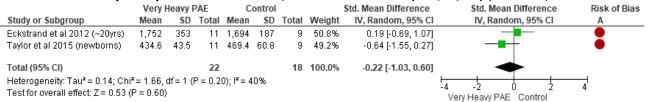
Notes: CI: confidence interval; MD: mean difference; OR: odds ratio.

**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; f) 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 (cm<sup>3</sup>)

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



Risk of bias legend
(A) Overall RoB

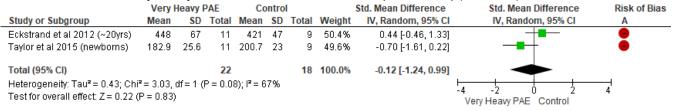
#### Confirmed PAE level unquantifiable and total brain/intracranial volume (cm³, m/SD) (3 studies)

					,		•	a	,, •= , (• ••••.	,
	Confirmed Unquantifiable						!	Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Aghamohammadi-Sereshki et al 2022 (~10 yrs)	1,489.57	114.32	30	1,543.66	179.01	50	26.1%	-0.34 [-0.79, 0.12]		?
Hendrickson et al 2017 (9-16yrs)	1,364	205	92	1,413	236	83	61.1%	-0.22 [-0.52, 0.08]	<b>=</b>	•
Infante et al 2017 (10-16yrs)	1,425.3217	208.1406	18	1,493.9346	179.5753	19	12.8%	-0.35 [-1.00, 0.30]		•
Total (95% CI)	0.000.17.000		140			152	100.0%	-0.27 [-0.50, -0.04]	. •	
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 0.24$ , $df = 2$ (P = Test for overall effect: $Z = 2.26$ (P = 0.02)	= 0.89); I*= 0%							Confirme	4 -2 0 2 d Unquantifiable Control	4

Risk of bias legend
(A) Overall RoB

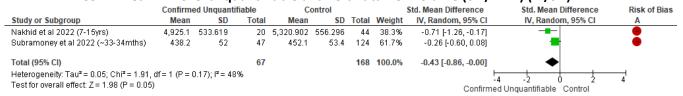
#### White Matter Volume (cm<sup>3</sup>)

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



#### Left Putamen Volume (cm<sup>3</sup>/mm<sup>3</sup>)

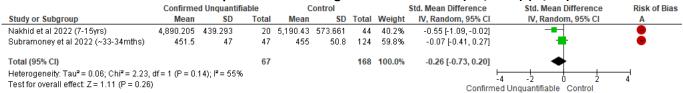
#### Confirmed PAE level unquantifiable and Left Putamen volume (cm/mm³) (m/SD)



Risk of bias legend
(A) Overall RoB

#### Right Putamen Volume (cm<sup>3</sup>/mm<sup>3</sup>)

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



Risk of bias legend
(A) Overall RoB

#### Left Amygdala Volume (mm³)

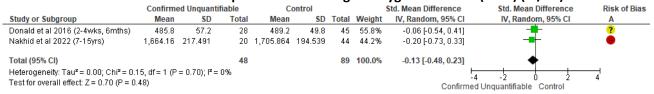
#### Confirmed PAE level unquantifiable and Left Amygdala volume (mm³) (m/SD)

	Confirme	ed Unquanti	•	Control				Std. Mean Difference	Std. Mean Difference	Risk of Bia
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Donald et al 2016 (2-4wks, 6mths)	552	65.9	28	559.7	44.6	45	56.3%	-0.14 [-0.61, 0.33]	-	?
Nakhid et al 2022 (7-15yrs)	1,477	142.947	20	1,579	221.975	44	43.7%	-0.50 [-1.04, 0.04]	-	•
Total (95% CI)			48			89	100.0%	-0.30 [-0.65, 0.06]	•	
Heterogeneity: Tau² = 0.00; Chi² = 0.9		= 0.32); l²=	0%					-4	-2 0 2	<u></u>
Test for overall effect: $Z = 1.65$ (P = 0.	10)							Confirmed	Unquantifiable Control	•

Risk of bias legend (A) Overall RoB

#### Right Amygdala Volume (mm<sup>3</sup>)

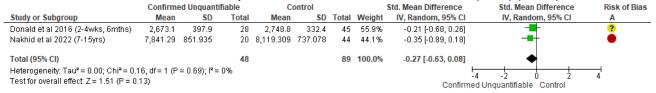
#### Confirmed PAE level unquantifiable and Right Amygdala volume (mm³) (m/SD)



Risk of bias legend (A) Overall RoB

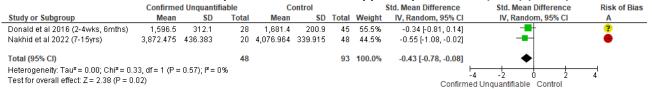
#### Left Thalamus Volume (mm<sup>3</sup>)

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



#### Left Hippocampus Volume (mm<sup>3</sup>)

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

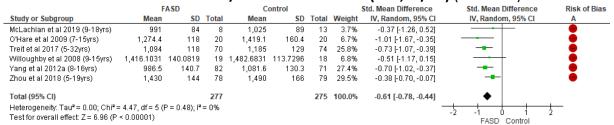


Risk of bias legend
(A) Overall RoB

#### **Diagnosed Studies**

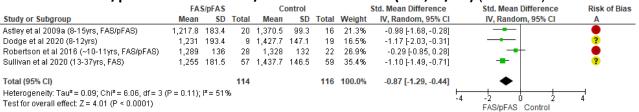
#### Total brain/intracranial volume (cm<sup>3</sup>)

#### FASD and total brain/intracranial volume (cm<sup>3</sup>, m/SD) (6 studies)



Risk of bias legend

#### FAS/pFAS and total brain/intracranial volume (cm<sup>3</sup>, m/SD) (4 studies)



Risk of bias legend
(A) Overall RoB

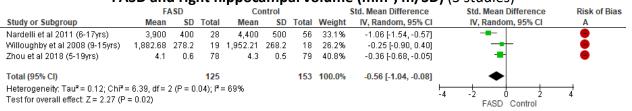
#### ARND/Others and total brain/intracranial volume (cm³, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

#### Right hippocampal volume (mm<sup>3</sup>)

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

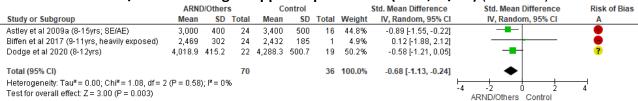


#### FAS/pFAS and right hippocampal volume (mm³, m/SD) (3 studies)

	FA:	S/pFAS		C	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Astley et al 2009a (8-15yrs, FAS/pFAS)	2,900	500	20	3,400	500	16	52.7%	-0.98 [-1.68, -0.28]	-	
Biffen et al 2017 (9-11yrs, heavily exposed)	2,266	318	28	2,432	185	1	6.5%	-0.51 [-2.51, 1.49]	<del></del>	•
Dodge et al 2020 (8-12yrs)	4,183.3	391.5	9	4,288.3	500.7	19	40.8%	-0.22 [-1.01, 0.58]	-	?
Total (95% CI)			57			36	100.0%	-0.64 [-1.15, -0.13]	•	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.00, df = 2	(P = 0.37)	$); I^2 = 0^9$	%						<del>, , , , , , , , , , , , , , , , , , , </del>	<del></del>
Test for overall effect: Z = 2.46 (P = 0.01)								,	FAS/nFAS Control	4

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

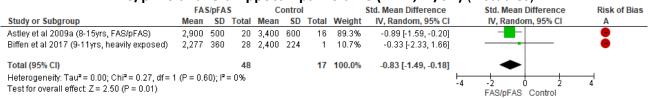
#### Left hippocampal volume (mm<sup>3</sup>)

#### FASD and left hippocampal volume (mm<sup>3</sup>, m/SD) (4 studies)

			_			_		\ , , , - ,	\		
	1	FASD		C	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α	
Dodge et al 2020 (8-12yrs)	4,257.3	514.3	9	4,290.6	517.5	19	14.9%	-0.06 [-0.86, 0.73]	_	?	
Nardelli et al 2011 (6-17yrs)	3,900	400	28	4,400	500	56	27.6%	-1.06 [-1.54, -0.57]		•	
Willoughby et al 2008 (9-15yrs)	1,889.7	227.86	19	2,036.39	249.06	18	19.2%	-0.60 [-1.26, 0.06]	<del></del>	•	
Zhou et al 2018 (5-19yrs)	4,100	700	78	4,400	500	79	38.3%	-0.49 [-0.81, -0.17]	-		
Total (95% CI)			134			172	100.0%	-0.60 [-0.96, -0.25]	•		
Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup>			.13); I²	= 47%					-4 -2 0 2	4	
Test for overall effect: Z = 3.30 (P	= 0.0010)								FASD Control		

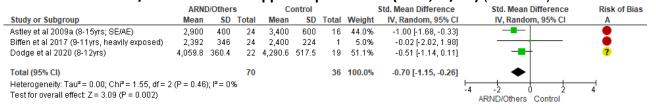
Risk of bias legend
(A) Overall RoB

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



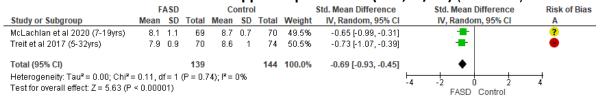
Risk of bias legend (A) Overall RoB

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



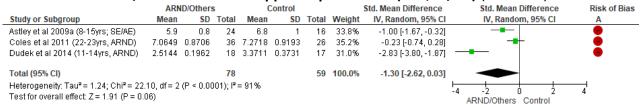
#### Total hippocampal volume (cm<sup>3</sup>)

#### FASD and total hippocampal volume (cm<sup>3</sup>, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

#### ARND/Others and total hippocampal volume (cm<sup>3</sup>, m/SD) (3 studies)



Risk of bias legend (A) Overall RoB

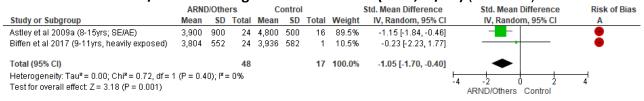
#### Right caudate volume (mm<sup>3</sup>)

#### FAS/pFAS and right caudate volume (mm<sup>3</sup>, m/SD) (4 studies)

,			-0					1 ,, ,	(	
	FASD			Control				Std. Mean Difference	Std. Mean Difference	Risk of Bia
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Astley et al 2009a (8-15yrs, FAS/pFAS)	3,800	500	19	4,800	500	16	27.6%	-1.95 [-2.78, -1.13]	<del></del>	•
Biffen et al 2017 (9-11yrs, heavily exposed)	3,662	607	28	3,936	582	1	13.9%	-0.44 [-2.44, 1.56]		•
Joseph et al 2014 (FAS/pFAS)	3,840	704	12	4,265	624	19	28.7%	-0.63 [-1.37, 0.11]	<del></del>	•
Suttie et al 2018 (FAS)	3,361	693	22	4,713	499	47	29.9%	-2.36 [-3.01, -1.71]	-	
Total (95% CI)			81			83	100.0%	-1.49 [-2.45, -0.52]	•	
Heterogeneity: Tau <sup>2</sup> = 0.69; Chi <sup>2</sup> = 13.75, df =	3 (P = 0	.003);	$I^2 = 78$	%					1 <del>4 5 1 5</del>	$\rightarrow$
Test for overall effect: $Z = 3.03$ (P = 0.002)									FASD Control	4

Risk of bias legend
(A) Overall RoB

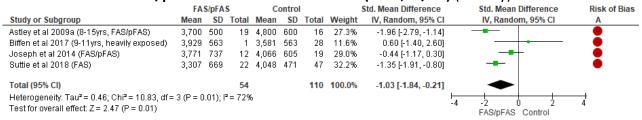
#### ARND/Others and right caudate volume (mm³, m/SD) (2 studies)



Risk of bias legend (A) Overall RoB

#### Left caudate volume (mm<sup>3</sup>)

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



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

	ARNI	)/Othe	ers	C	ontrol	l		Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Astley et al 2009a (8-15yrs; SE/AE)	3,900	900	24	4,800	600	16	89.6%	-1.11 [-1.79, -0.43]		•
Biffen et al 2017 (9-11yrs, heavily exposed)	3,798	543	24	3,929	563	1	10.4%	-0.23 [-2.23, 1.77]		•
Total (95% CI)			48			17	100.0%	-1.02 [-1.66, -0.37]	•	
Heterogeneity: Tau $^2$ = 0.00; Chi $^2$ = 0.66, df = $^4$ Test for overall effect: Z = 3.09 (P = 0.002)	(P = 0.4	2); l² =	= 0%						-4 -2 0 2 ARND/Others Control	<u></u>

Risk of bias legend
(A) Overall RoB

#### Total caudate volume (mm<sup>3</sup>)

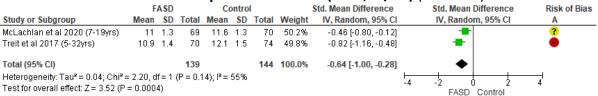
#### FASD and total caudate volume (mm<sup>3</sup>, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

#### Total putamen volume (mm<sup>3</sup>)

#### FASD and total putamen volume (mm<sup>3</sup>, m/SD) (2 studies)



Risk of bias legend (A) Overall RoB

#### Right putamen volume (mm<sup>3</sup>)

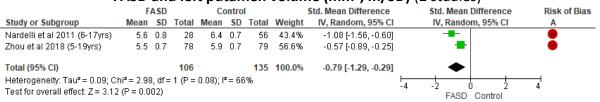
#### FASD and right putamen volume (mm<sup>3</sup>, m/SD) (2 studies)

	_		U			_		- ( , , , -	, ,	-,	
	FASD Control							Std. Mean Difference	Std. Mean	Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	Α
Nardelli et al 2011 (6-17yrs)	5.3	0.7	28	6.2	0.6	56	47.2%	-1.41 [-1.91, -0.90]	-		•
Zhou et al 2018 (5-19yrs)	5.4	0.7	78	5.8	0.7	79	52.8%	-0.57 [-0.89, -0.25]	-		•
Total (95% CI)			106			135	100.0%	-0.96 [-1.78, -0.14]	•		
Heterogeneity: Tau <sup>2</sup> = 0.30; C Test for overall effect: Z = 2.31		•	= 1 (P =	0.006);	<b>2</b> = 8	37%			-4 -2 (FASD	) 2 Control	4

Risk of bias legend
(A) Overall RoB

#### Left putamen volume (mm<sup>3</sup>)

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



# Corpus callosum volume (mm<sup>3</sup>)

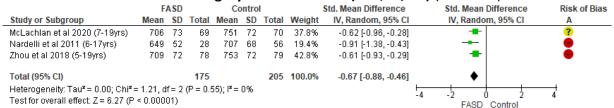
# FAS/pFAS and corpus callosum volume (mm³, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

# Total Grey Matter Volume (cm<sup>3</sup>)

## FASD and total grey matter volume (cm<sup>3</sup>, m/SD) (3 studies)



Risk of bias legend
(A) Overall RoB

#### Cortical Grey Matter Volume (cm<sup>3</sup>)

# FASD and cortical grey matter volume (cm<sup>3</sup>, m/SD) (2 studies)

				- 0	., -			, , , , , , , , , , , , , , , , , , , ,	,	/ (= = = = = = = )	
	F	ASD		Co	ntro	I		Std. Mean Difference		Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
McLachlan et al 2019 (9-18yrs)	502	38	8	532	38	13	11.8%	-0.76 [-1.67, 0.16]			•
Treit et al 2017 (5-32yrs)	496	68	70	540	63	74	88.2%	-0.67 [-1.00, -0.33]			•
Total (95% CI)			78			87	100.0%	-0.68 [-0.99, -0.36]		•	
Heterogeneity: Tau² = 0.00; Chi²			(P = 0.3)	86); I²=	0%				-4	-2 1 2	<u></u>
Test for overall effect: $Z = 4.22$ (P	< 0.000	1)								FASD Control	•

Risk of bias legend
(A) Overall RoB

# Total Subcortical Grey Matter Volume (cm<sup>3</sup>)

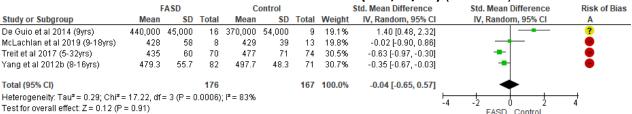
#### FASD and total subcortical grey matter volume (cm<sup>3</sup>, m/SD) (4 studies)

					_	•		•	•	, , ,	,
	F	ASD		Co	ontro	I		Std. Mean Difference		Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
McLachlan et al 2019 (9-18yrs)	61	4.7	8	64	3.6	13	6.2%	-0.71 [-1.63, 0.20]			•
McLachlan et al 2020 (7-19yrs)	47	4.8	69	51	4.3	70	35.1%	-0.87 [-1.22, -0.52]		-	?
Nardelli et al 2011 (6-17yrs)	45	6	28	52	5	56	19.3%	-1.30 [-1.79, -0.80]			•
Zhou et al 2018 (5-19yrs)	186	20	78	201	20	79	39.3%	-0.75 [-1.07, -0.42]		-	•
Total (95% CI)			183			218	100.0%	-0.90 [-1.13, -0.66]		•	
Heterogeneity: Tau² = 0.01; Chi²:	= 3.49, d	f= 3	(P = 0.3)	32); I²=	14%				<u> </u>	-2 1 2	<del></del>
Test for overall effect: $Z = 7.57$ (P	< 0.000	01)							-4	FASD Control	4

Risk of bias legend (A) Overall RoB

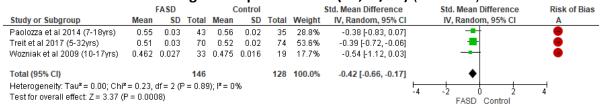
#### Total White Matter Volume (cm<sup>3</sup>)

## FASD and total white matter volume (cm<sup>3</sup>, m/SD) (4 studies)



#### Genu Corpus Callosum (FA)

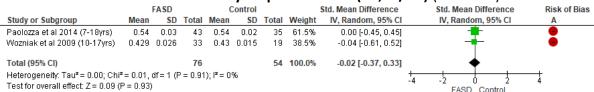
# FASD and genu corpus callosum (FA, m/SD) (3 studies)



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)

				•		•	` '	, , ,
	FA	SD	Co	ontrol			Std. Mean Difference	Std. Mean Difference Risk of Bias
Study or Subgroup	Mean	SD Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Paolozza et al 2014 (7-18yrs)	0.55	0.03 43	0.55	0.02	35	61.5%	0.00 [-0.45, 0.45]	<del></del>
Wozniak et al 2009 (10-17yrs)	0.424 0.	025 33	0.424	0.02	19	38.5%	0.00 [-0.56, 0.56]	+ •
Total (95% CI)		76			54	100.0%	0.00 [-0.35, 0.35]	<b>+</b>
Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 0.00 (f		= 1 (P = 1.00	)); I <b>*</b> = 09	%				-4 -2 0 2 4 FASD Control

Risk of bias legend
(A) Overall RoB

## Posterior Midbody Corpus Callosum (FA)

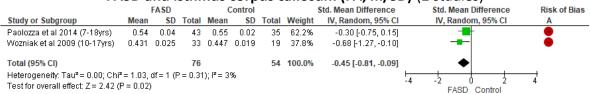
#### FASD and posterior midbody corpus callosum (FA, m/SD) (2 studies)

		FASD		(	Control			Std. Mean Difference	Std. Me	an Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rar	dom, 95% CI	Α
Paolozza et al 2014 (7-18yrs)	0.54	0.04	43	0.55	0.02	35	62.5%	-0.30 [-0.75, 0.15]		-	
Wozniak et al 2009 (10-17yrs)	0.424	0.026	33	0.441	0.022	19	37.5%	-0.68 [-1.26, -0.10]	-	<b>-</b>	•
Total (95% CI)			76			54	100.0%	-0.44 [-0.80, -0.09]		•	
Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 2.44 (f		,	° = 0.32	?); I² = 1	%				-4 -2 FAS	0 2 SD Control	4

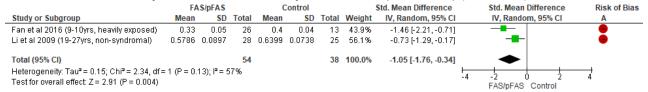
Risk of bias legend (A) Overall RoB

#### Isthmus Corpus Callosum (FA)

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



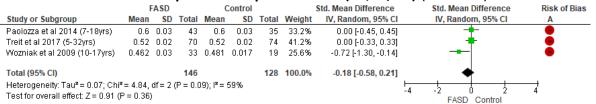
# FAS/pFAS and Isthmus corpus callosum (FA, m/SD) (2 studies)



Risk of bias legend (A) Overall RoB

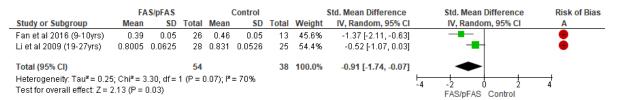
#### Splenium Corpus Callosum (FA)

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



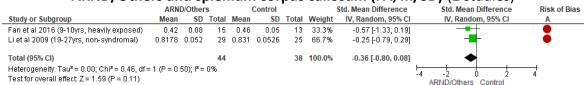
Risk of bias legend (A) Overall RoB

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



Risk of bias legend (A) Overall RoB

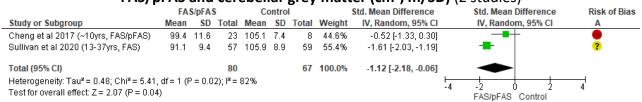
#### ARND/Others and splenium corpus callosum (FA, m/SD) (2 studies)



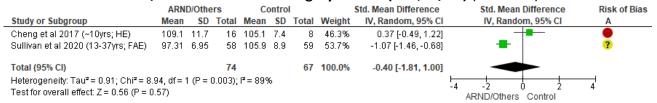
Risk of bias legend
(A) Overall RoB

#### Cerebellar grey matter (cm<sup>3</sup>)

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



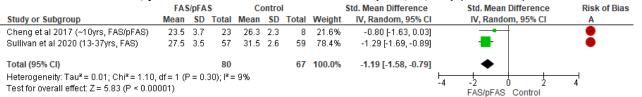
# ARND/Others and cerebellar grey matter (cm<sup>3</sup>, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

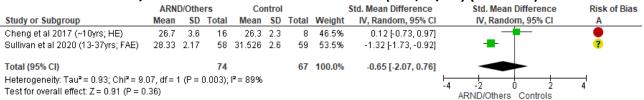
# Cerebellar white matter (cm<sup>3</sup>)

# 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 (cm<sup>3</sup>)

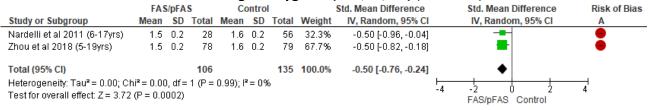
# FASD and left amygdala (cm³, m/SD) (2 studies)

	F	ASD		Co	ontro	I		Std. Mean Difference		Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Nardelli et al 2011 (6-17yrs)	1.4	0.2	28	1.6	0.3	56	31.6%	-0.73 [-1.20, -0.26]		-	
Zhou et al 2018 (5-19yrs)	1.4	0.2	78	1.5	0.2	79	68.4%	-0.50 [-0.82, -0.18]		-	•
Total (95% CI)			106			135	100.0%	-0.57 [-0.83, -0.31]		•	
Heterogeneity: Tau² = 0.00; C Test for overall effect: Z = 4.26				0.42); f	²= 09	%			-4	-2 0 2 FASD Control	4

Risk of bias legend
(A) Overall RoB

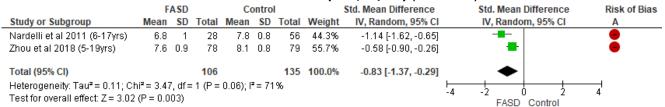
## Right amygdala (cm<sup>3</sup>)

# FASD and right amygdala (cm<sup>3</sup>, m/SD) (2 studies)



# Left thalamus (cm<sup>3</sup>)

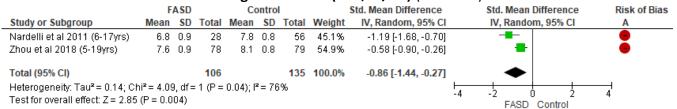
# FASD and left thalamus (cm<sup>3</sup>, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

# Right thalamus (cm<sup>3</sup>)

# FASD and right thalamus (cm<sup>3</sup>, m/SD) (2 studies)



Risk of bias legend
(A) Overall RoB

# Thalamus (cm<sup>3</sup>)

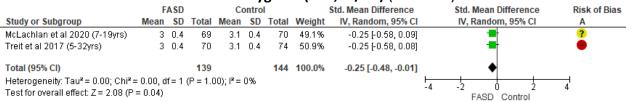
# FASD and thalamus (cm<sup>3</sup>, m/SD) (2 studies)

	F	ASD		Co	ontrol			Std. Mean Difference		Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
McLachlan et al 2020 (7-19yrs)	15.2	1.7	69	16.2	1.5	70	49.8%	-0.62 [-0.96, -0.28]		-	?
Treit et al 2017 (5-32yrs)	14.2	1.8	70	15.7	2	74	50.2%	-0.78 [-1.12, -0.44]		-	•
Total (95% CI)			139			144	100.0%	-0.70 [-0.94, -0.46]		•	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> : Test for overall effect: $Z = 5.72$ (P			(P = 0.5	51); I²=	0%				-4	-2 0 2 FASD Control	4

Risk of bias legend (A) Overall RoB

#### Amygdala (cm<sup>3</sup>)

# FASD and amygdala (cm<sup>3</sup>, m/SD) (2 studies)



# Summary of available outcomes for seizures

	9	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

<sup>\*</sup>adjusted for maternal age, gestational age, parity, household SES, prenatal smoking, maternal hx of epilepsy & time to pregnancy

# **GRADE** ratings for seizures

		Certai	nty assessmen	t		Nº of	patients	Effec	t	Certainty
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSUR	E STUDIES									
Risk of ne	onatal seizu	ıres								
≥ 1 binge	at 11-16 w	eeks								
1	not serious	not serious	not serious	serious <sup>e,f</sup>	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 <sup>d</sup>	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 <sup>d,e</sup>	none	210/ 20,95 5	700/34, 997	aIRR 1.08 (0.34 to 3.45)	-	⊕⊕⊕○ Moderate
Risk of Ep										
≥1 binge	at 11-16 w	eeks			_		_			
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 <sup>d</sup>	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 <sup>d</sup>	none	1,467 /20,9 55	2,800/3 4,997	aIRR <b>0.54</b> (0.25 to 1.14)	-	⊕⊕⊕○ Moderate

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

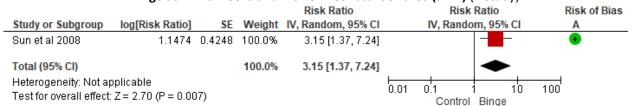
**Explanations:** a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ( $I^2 > 50\%$  and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no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

				Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Sun et al 2008	-0.2914	0.206	100.0%	0.75 [0.50, 1.12]			•
Total (95% CI)			100.0%	0.75 [0.50, 1.12]		. ◆	
Heterogeneity: Not ap Test for overall effect:		6)			0.01	0.1 1 10 Control Light PAE	100

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

Charles on Carlonna	In afficial Datio	er.	18/-:	Risk Ratio	Risk Ratio Risk of Bid	as
Study or Subgroup	log[Risk Ratio]	SE	weight	IV, Random, 95% CI	IV, Random, 95% CI A	
Sun et al 2008	0.0798	0.5911	100.0%	1.08 [0.34, 3.45]	<b>-</b>	
Total (95% CI)			100.0%	1.08 [0.34, 3.45]	<b>*</b>	
Heterogeneity: Not ap Test for overall effect:	•	3)			0.01 0.1 1 10 100 Control Moderate PAE	

## Epilepsy Risk (aIRR)

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

	J			Risk Ratio		Risk R	atio		Risk of Bias
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI		IV, Randon	n, 95% CI		Α
Sun et al 2008	0.5933	0.2404	100.0%	1.81 [1.13, 2.90]					•
Total (95% CI)			100.0%	1.81 [1.13, 2.90]			•		
Heterogeneity: Not ap Test for overall effect:	•	)			0.01	0.1 1	10 Pings	100	

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

	•	•		Risk Ratio	• `	Risk	Ratio		Risk of Bias
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI		Α
Sun et al 2008	-0.0896	0.0943	100.0%	0.91 [0.76, 1.10]					•
Total (95% CI)			100.0%	0.91 [0.76, 1.10]		•			
Heterogeneity: Not ap Test for overall effect	• •	1)			0.01	0.1 1	10 Light PAF	100	

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

				Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	IV, F	Random, 95% CI	Α
Sun et al 2008	-0.6254	0.3864	100.0%	0.54 [0.25, 1.14]			•
Total (95% CI)			100.0%	0.54 [0.25, 1.14]		<b>◆</b>	
Heterogeneity: Not ap Test for overall effect:	•	)			0.01 0.1 Co	1 10 ontrol Moderate P	100 AE

# 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					

<sup>\*</sup>adjusted for term births, Aboriginal status (outcome here non-Aboriginal only), appropriate fetal growth, ilicit 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

		Certa	ainty assessmen	τ		и₅ от b	atients	ETT	ect	Certainty	
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)		
EXPOSUR	EXPOSURE STUDIES										
Pre/perina	atal acquire	ed CP									
Confirme	d unquanti	fied									
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e</sup>	none	13,807	40,148	<b>aOR 3.32</b> (1.30 to 8.48)	-	⊕⊕○○ Low	
All CP type	es										
Confirme	d unquanti	fied									
1	serious <sup>a</sup>	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

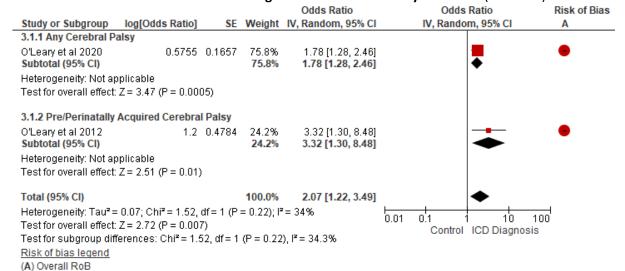
**Explanations:** a) >50% of studies were rated as moderate or high risk of bias; b) High heterogeneity ( $I^2 > 50\%$  and significant chi-square for heterogeneity); c) >50% of studies had a sample not representative of the Australian populations; d) 95% CI for overall estimate crossed the line of no 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 <sup>a</sup>	Frequency	1 study: Light, Moderate, Heavy PAE						
Diagnosed	Visual acuity ≤ 0.2	Frequency	1 study: FAS						

<sup>&</sup>lt;sup>a</sup> not defined

# GRADE ratings for visual impairment

		Cert	ainty assessmer	nt		Nº of p	atients	Eff	ect	Certainty
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSUR	RE STUDIES									
Frequenc	y of Severe	Visual Acuity (0.1	to <0.5)							
Very Hea	vy PAE									
1	serious <sup>a</sup>	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	43	55	OR 1.29 (0.08 to 21.16)	-	⊕○○○ Very Low
Frequenc	y of Abnorr	nal Visual Abilitie	s							
Light PAE										
1	serious <sup>a</sup>	not serious	not serious	serious <sup>d,f</sup>	none	18/675	19/758	OR 1.07 (0.55 to 2.05)	-	⊕⊕○○ Low
Moderat	e PAE				•	•				
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	8/175	19/758	OR 1.86 (0.80 to 4.33)	-	⊕○○○ Very Low
Heavy PA	ΛE			L				·		
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	2/20	19/758	OR 4.32 (0.94 to 19.96)	-	⊕○○○ Very Low
DIAGNOS	ED STUDIE	S								
Frequenc	y of Visual	Acuity (<2.0)								
FAS										
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	-	4/30	0/22	OR 7.64 (0.39 to 149.74)	-	⊕○○○ Very Low

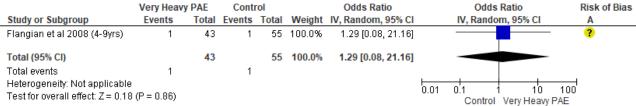
Notes: CI: confidence interval; MD: mean difference; OR: odds ratio

**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)

	Light P	AE	Conti	rol		Odds Ratio	Odds Ratio Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI A
Falgreen Erikson 2012 (5.2yrs)	18	675	19	758	100.0%	1.07 [0.55, 2.05]	1 •
Total (95% CI)		675		758	100.0%	1.07 [0.55, 2.05]	1 ♦
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.19 (P :	18 = 0.85)		19				0.001 0.1 1 10 1000 Control Light PAE

Risk of bias legend (A) Overall RoB

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

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	Moderate PAE		Control			Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Falgreen Erikson 2012 (5.2yrs)	8	175	19	758	100.0%	1.86 [0.80, 4.33]	+
Total (95% CI)		175		758	100.0%	1.86 [0.80, 4.33]	•
Total events	8		19				
Heterogeneity: Not applicable							0.01 0.1 1 10 100
Test for overall effect: $Z = 1.45$ (P	= 0.15)						Control Moderate PAE

Risk of bias legend (A) Overall RoB

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

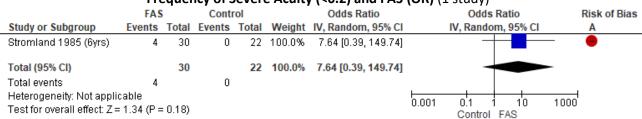
	,						( ) ( )
	Heavy PAE Control				Odds Ratio	Odds Ratio Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Falgreen Erikson 2012 (5.2yrs)	2	20	19	758	100.0%	4.32 [0.94, 19.96]	•
Total (95% CI)		20		758	100.0%	4.32 [0.94, 19.96]	-
Total events	2		19				
Heterogeneity: Not applicable							0.01 0.1 1 10 100
Test for overall effect: Z = 1.87 (P	= 0.06)						Control Heavy PAE

Risk of bias legend (A) Overall RoB

## Diagnosed studies

# Visual Acuity (Frequency/OR)

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



# Summary of available outcomes for hearing loss

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

<sup>&</sup>lt;sup>a</sup> not defined

# GRADE ratings for hearing loss

		Certai	nty assessment			Nº of pa	atients		Effect	Certainty		
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)			
EXPOSU	EXPOSURE STUDIES											
Frequency of abnormal hearing abilities												
Light												
1	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	40/675	28/785	OR 1.7 (1.04 to 2.79)	-	⊕⊕○○ Low		
Moderat	e											
1	serious <sup>a</sup>	not serious	not serious	serious <sup>d,f</sup>	none	7/175	28/785	OR 1.13 (0.48 to 2.26)	-	⊕⊕○○ Low		
Heavy												
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	3/20	28/785	OR 4.77 (1.32 to 17.23)	-	⊕○○○ Very Low		
Hearing i	impairment	(aOR)										
Any PAE												
1	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>d,e</sup>	none	10,	562	<b>aOR 1.49</b> (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 (I² >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.

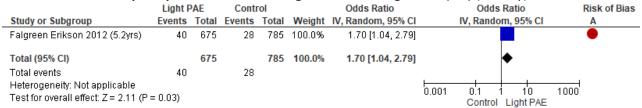
<sup>&</sup>lt;sup>b</sup> defined as children receiving medical treatment for hearing impairment congenital or definitive cases of hearing impairment

<sup>&</sup>lt;sup>c</sup> adjusted for child sex, birth order, birth weight, history of otitis media, mothers age at pregnancy, familial history of hearing impairment, prenatal smoking

# 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)

•	Heavy	PAE	Conti	rol	_	Odds Ratio	Odds Ratio Risk o	of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI A	
Falgreen Erikson 2012 (5.2yrs)	3	20	28	785	100.0%	4.77 [1.32, 17.23]	- <mark>  -</mark>   -	
Total (95% CI)		20		785	100.0%	4.77 [1.32, 17.23]	•	
Total events	3		28					
Heterogeneity: Not applicable Test for overall effect: Z = 2.39 (P :	= 0.02)						0.001 0.1 1 10 1000 Control Heavy PAE	

Risk of bias legend
(A) Overall RoB

# Hearing Impairment (OR)

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

