# Supplemental File E GRADE ratings and meta-analyses for dysmorphology outcomes

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		<b>3</b> Sentinel Facial Feature	es		
Study Type	Outcome	Data	# of studies		
	Philtrum Measures	Philtrum Smoothness (3 or	4 studies: 1 moderate, 1 very heavy PAE, 3		
		4+) (%)	confirmed unquantified PAE		
		Philtrum Rank (1-5) (m/SD)	<b>1 study</b> with confirmed but unquantified PAE		
		Philtrum Length (mm)	<b>1</b> study with heavy PAE, varying exposure		
		(m/SD)	throughout pregnancy		
		Long Philtrum (%)	<b>1 study</b> with moderate PAE and very heavy PAE		
		Hypoplastic philtrum (%)	1 study with any PAE		
	Vermilion Measures	Vermilion Thinness (3 or 4+)	<b>4 studies:</b> 1 moderate, 1 very heavy, 3 confirmed		
Exposure		(%)	unquantified PAE		
Studies		Vermilion Rank (1-5) (m/SD)	1 study with confirmed unquantified PAE		
		Thin upper lip (%)	<b>2</b> studies: 1 heavy PAE and 1 confirmed unquantifiable PAE		
	Palpebral Fissure	Short PFL (%)	<b>7 studies:</b> 1 moderate, 1 heavy PAE, 1 very heavy,		
	Measures		5 confirmed unquantified		
		PFL Length (mm) m/SD	2 studies: with 1 heavy PAE, 1 confirmed		
			unquantified PAE		
		PFL (centile)	1 study confirmed unquantifiable PAE		
		PFL (z-score)	0 studies		
	Philtrum Measures	Philtrum Smoothness (4+) (%)	<b>20 studies:</b> 6 FASD, 12 FAS, 10 pFAS, 9 ARND/other		
		Philtrum Rank (1-5) (mean/SD)	<b>3 studies:</b> 2 FASD, 1 FAS/pFAS		
		Philtrum Length (mm) (m/SD)	6 studies: 2 FASD, 3 FAS, 3 pFAS, 2 ARND/Others		
		Long Philtrum (%)	<b>3 studies:</b> 1 FASD, 1 FAS, 2 FAS/pFAS		
Diagnosed		'Other' Measures	<b>1 study</b> with z-scores (FASD) <b>1 study</b> with philtrum depth (mm) (FASD)		
Studies	Vermilion Measures	Vermilion Thinness (4+) (%)	<b>19 studies:</b> 5 FASD, 12 FAS, 9 pFAS, 9 ARND/Other		
		Vermilion Rank (1-5) (m/SD)	<b>2 studies:</b> 1 FASD and 1 FAS/pFAS		
		Upper lip circularity (m/SD)	1 study FASD		
	Palpebral Fissure	Short PFL (%) <3 <sup>rd</sup> centile	<b>4 studies:</b> 1 FASD, 3 FAS, 3 pFAS, 3 ARND/Other		
	Measures	Short PFL (%) <10 <sup>th</sup> centile	<b>8 studies:</b> 1 FASD, 7 FAS, 4 pFAS, 6 ARND/Other		
		PFL (mm)			
		PFL (centile)	<b>11 studies:</b> 5 FASD, 5 FAS, 4 pFAS, 2 ARND/Other		
		PFL (z-score)	7 studies: 1 FASD, 5 FAS, 6 pFAS, 5 ARND 2 studies: 1 FAS, 2 pFAS, 1 ARND/ Others		
	1	FIL (2-SCOLE)	2 Studies. I FAS, 2 PFAS, I ARIND/ Utilets		

# Summary of available outcomes for 3 sentinel facial features

# GRADE ratings for 3 sentinel facial features

№ of studiesRisk of biasEXPOSURESTUDIEPHILTRUMMEASUPhiltrumSmoothnModeratePAE (3+1seriouVery HeavyPAE (31seriouConfirmed unquar	ES JRES ess (3 or 4+) (% ) s <sup>a</sup> not seriou		Imprecision	Other considerati ons	PAE	Control	Relative (95% Cl)	Absolute (95% Cl)	Certainty
PHILTRUM MEASU Philtrum Smoothn Moderate PAE (3+ 1 seriou Very Heavy PAE (3 1 seriou	JRES ess (3 or 4+) (% ) s <sup>a</sup> not seriou								
Philtrum Smoothn Moderate PAE (3+ 1 seriou Very Heavy PAE (3 1 seriou	ess (3 or 4+) (% ) s <sup>a</sup> not seriou								
Moderate PAE (3+ 1 seriou Very Heavy PAE (3 1 seriou	) s <sup>a</sup> not seriou								
1 seriou Very Heavy PAE (3 1 seriou	s <sup>a</sup> not seriou	s not serious							
Very Heavy PAE (3		s not serious		•					
1 seriou	+)		serious <sup>e,f</sup>	none	45	253	<b>OR 3.26</b> (1.36 to 7.82)	-	⊕⊕⊖⊖ Low
				-					
Confirmed unquar		s not serious	serious <sup>e,f</sup>	none	19	253	<b>OR 6.03</b> (2.05 to 17.74)	-	⊕⊕⊖⊖ Low
					1-				
3 seriou	s <sup>a</sup> not serious	s not serious	serious <sup>e,f</sup>	none	174/344 (50.6%)	43/316 (13.6%)	<b>OR 6.24</b> (4.22 to 9.22)	<b>360 more per</b> <b>1,000</b> (from 263 more to 456 more)	⊕⊕⊖⊖ Low
Philtrum Rank (1-5	5) (m/SD)								
Confirmed unquar	ntifiable								
1 seriou	s <sup>a</sup> not seriou	s not serious	serious <sup>e,f</sup>	none	65	55	-	SMD 0.7 higher (0.33 higher to 1.07 higher)	⊕⊕⊖⊖ Low
Philtrum Length (n	nm) (m/SD)								
Heavy									
1 seriou	s <sup>a</sup> not seriou	s not serious	serious <sup>e,f</sup>	none	16	48	-	SMD 1.34 higher (0.73 higher to 1.96 higher)	⊕⊕⊖⊖ Low
Long Philtrum (%)									
Moderate									
1 seriou	s <sup>a</sup> not seriou	s not serious	very serious <sup>d,e,</sup>	<sup>f</sup> none	7/45	20/253	<b>OR 2.15</b> (0.85 to 5.42)	-	⊕○○○ Very Low
Very Heavy									
1 seriou	s <sup>a</sup> not seriou	s not serious	very serious <sup>d,e,</sup>	<sup>f</sup> none	19	253	<b>OR 2.18</b> (0.59 to 8.14)	-	⊕○○○ Very Low
Hypoplastic Philtru	ım (%)								
Any PAE									
1 seriou		s not serious	very serious <sup>d,e,</sup>	<sup>f</sup> none	12	12	<b>OR 18.33</b> (0.88 to 380.70)	-	⊕○○○ Very Low
VERMILION MEAS									
Vermilion Thinnes									
Moderate PAE (3+	-			1				•	
1 seriou		s not serious	very serious <sup>d,e,f</sup>	none	11/45	40/253	<b>OR 1.72</b> (0.82 to 3.68)	-	⊕○○○ Very Low
Very Heavy PAE (3		<u> </u>		6	<i>c.k.c</i>	40/0-0	0.0.11	r	
1 seriou	s <sup>a</sup> not seriou	s not serious	very serious <sup>d,e,</sup>	<sup>f</sup> none	6/19	40/253	<b>OR 2.46</b> (0.88 to 6.85)	-	⊕○○○ Very Low
Confirmed unquar	ntifiable (4+)			1		1			
3 seriou	s <sup>a</sup> not seriou	s not serious	serious <sup>f</sup>	none	162/334 (48.5%)	46/316 (14.6%)	<b>OR 5.28</b> (3.6 to 7.74)	<b>328 more per</b> <b>1,000</b> (from 235 more to 423 more)	⊕⊕⊖⊖ Low
Vermilion Rank (1-	5) (m/SD)								

Confirmed	unquantifi	iable								
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	65	56	-	SMD 0.57 higher (0.20 higher to 0.93 higher)	⊕⊕⊖⊖ Low
hin upper										
eavy PAE			1						· · · · ·	
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	10/52	1/48	<b>OR 11.19</b> (1.37 to 91.14)	-	⊕⊕⊖⊖ Low
	Unquantif					12	42	00.0.21 /0.42		
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	12	12	<b>OR 9.21</b> (0.42 to 200.59)	-	⊕○○○ Very Low
		MEASURES					•			
hort PFL <	3 <sup>rd</sup> or <10 <sup>t</sup>	<sup>th</sup> (%)								
loderate	PAE (<10 <sup>th</sup> )	)								
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	14/45	13/253	<b>OR 8.34</b> (3.59 to 19.39)	-	⊕⊕⊖⊖ Low
eavy PAE										
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	6/52	0/48	<b>OR 13.56</b> (0.74 to 247.52)	-	⊕○○○ Very Low
	/ PAE (<10 <sup>t</sup>			eesters of	<b></b>	C/40	12/252	00 0 52 /2 72		
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	6/19	13/253	<b>OR 8.52</b> (2.79 to 26.03)	-	⊕⊕⊖⊖ Low
onfirmed	unquantifi	iable	1							
5	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	156/421 (37.1%)	22/415 (5.3%)	<b>OR 9.15</b> (4.87 to 17.19)	<b>286 more per</b> <b>1,000</b> (161 more to 437 more)	⊕⊕⊖⊖ Low
alpebral F	issure Len	gth (mm) (m/SI	)	<u> </u>		•	1		,	
eavy PAE	(1 <sup>st</sup> trimes	ter)								
1	serious <sup>a</sup>	not serious	not serious	serious <sup>d,f</sup>	none	16	48	-	MD 0.11 higher (0.02 lower to 0.24 higher)	⊕⊕⊖⊖ Low
onfirmed	but Unqua	antifiable							012 1 1181101 /	
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	67	58	-	MD 1.40 lower (2.0 lower to 0.0.8 lower)	⊕⊕⊖⊖ Low
alpebral F	issure (cer	ntile) (m/SD)								
onfirmed	but Unqua	antifiable								
1	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	65	56	-	MD 15.7 lower (21.95 lower to 9.45 lower)	⊕⊕⊖⊖ Low
IAGNOSE	D STUDIES	6				•		1		
HILTRUM	MEASURE	S								
hiltrum Sr	moothness	5 (4+) (%)								
ASD										
6	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	none	106/191 (55.5%)	63/355 (17.7%)	<b>OR 6.86</b> (2.67 to 17.62)	<b>419 more per</b> <b>1,000</b> (from 188 more to 614 more)	⊕○○○ Very Low
AS	,		1				<b>.</b> .	-	· · · ·	
12	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	403/511 (78.86%)	542/268 6 (20.18%	(8.21 to		⊕○○○ Very Low
			1			1	1 )	1		

10	serious <sup>a</sup>	serious <sup>b</sup>	not serious							
			not serious	serious <sup>e</sup>	none	299/357 (83.75%)	505/248 8 (20.20%	(11.00 to	-	⊕○○○ Very Low
ARND/Oth	ers						)			
9	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>d</sup>	none	107/456 (23.5%)	380/217 5 (17.5%)	<b>OR 1.22</b> (0.74 to 2.00)	<b>31 more per</b> <b>1,000</b> (from 39 fewer to 123 more)	⊕○○○ Very low
hiltrum R	ank (1-5) (9	%) (m/SD)		<u> </u>						
ASD Diagi	nosis									
3	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	108	94	-	SMD 0.53 higher (0.26 higher to 0.80 higher)	⊕⊕⊖⊖ Low
hiltrum Lo	ength (mm	) (m/SD)								
ASD										
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	none	43	150	-	<b>MD 0.08 higher</b> (1.78 lower to 1.94 higher)	⊕○○○ Very low
AS						1				
3	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>d,e</sup>	none	187	381	-	MD 0.27 higher (0.26 lower to 0.79 higher)	⊕○○○ Very low
FAS										
3	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>d,e</sup>	none	105	284	-	MD 0.52 higher (0.21 lower to 1.25 higher)	⊕○○○ Very low
RND/Oth	ers									
2	serious <sup>a</sup>	serious <sup>b</sup>	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	76	139	-	<b>MD 1.77 higher</b> (0.16 lower to 3.71 higher)	⊕○○○ Very low
ong Philtr	rum (%)									
ny FASD I	Diagnosis					-				
3	serious <sup>a</sup>	not serious	not serious	not serious	none	191	519	<b>OR 1.68</b> (1.17 to 2.41)	-	⊕⊕⊕⊖ Moderate
			n Length (z-so	core), Philtrum D	epth (mm)					
		gth (z-score)	1	· dof		1 10	24			
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	40	31	-	MD 0.07 lower (0.54 lower to 0.40 higher)	⊕○○○ Very low
ASD – Phi	iltrum Dep						•			
1	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	25	30	-	MD 0.36 lower (0.50 lower to 0.22 lower)	⊕⊕⊖⊖ Low
ERMILLIC	ON MEASU	RES								
ermilion <sup>-</sup>	Thinness (4	+) (%)								
ASD										
5	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	none	87/170 (51.2%)	44/272 (16.2%)	<b>OR 10.10</b> (4.09 to 24.9)	<b>499 more per</b> <b>1,000</b> (from 279 more to 666 more)	⊕○○○ Very low
AS									· I	
12	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	421/511 (82.38%)	468/263 4 (17.76%	(12.07 to	-	⊕○○○ Very low

								-		6
9	serious <sup>a</sup>	not serious	not serious	serious <sup>e</sup>	none	271/318 (85.22%)	429/225 7 (19%)		-	⊕⊕⊖⊖ Low
RND/Oth	ers							· · ·		
9	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	98/456 (21.5%)	361/212 3 (17.0%)	<b>OR 1.13</b> (0.83 to 1.53)	<b>18 more per</b> <b>1,000</b> (from 25 fewer to 69 more)	⊕⊕⊖⊖ Low
ermilion l	Rank (1-5)	(m/SD)								
ASD Diagr	nosis									
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	85	89	-	SMD 0.76 higher (0.45 higher to 1.08 higher)	⊕⊕⊖⊖ Low
	ircularity (I	m/SD)								
ASD	<u> </u>									
1	serious <sup>a</sup>	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	26	27	-	<b>MD 7.37 higher</b> (-10.40 lower to 25.14 higher)	⊕○○○ Very low
		MEASURES								
	of Short ar	nd Palpebral Fis	sures (%) <3 <sup>r</sup>	<sup>d</sup> centile						
ASD										
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	21	83	<b>OR 7.47</b> (2.49 to 22.48)	-	⊕⊕⊖⊖ Low
AS						1				
3	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	7/23 (30.4%)	51/1212 (4.2%)	<b>OR 10.48</b> (4.08 to 26.92)	<b>273 more per</b> <b>1,000</b> (from 110 more to 500 more)	⊕⊕⊖⊖ Low
FAS										
3	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	20/61 (32.8%)	51/1212 (4.2%)	<b>OR 11.04</b> (5.99 to 20.33)	<b>258 more per</b> <b>1,000</b> (from 166 more to 430 more)	⊕⊕⊖⊖ Low
RND/Oth	ers									
3	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/47 (2.1%)	51/1212 (4.2%)	<b>OR 1.22</b> (0.28 to 5.24)	<b>9 more per</b> <b>1,000</b> (from 30 fewer to 145 more)	⊕○○○ Very low
requency	of Short ar	nd Palpebral Fis	sures (%) <10	) <sup>th</sup> centile						
ASD										
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	40	39	<b>OR 0.31</b> (0.03 to 3.09)	-	⊕○○○ Very low
AS						1				
7	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	150/187 (80.2%)	134/155 9 (8.6%)	<b>OR 44.05</b> (26.4 to 73.5)	<b>720 more per</b> <b>1,000</b> (from 627 more to 788 more)	⊕⊕⊖⊖ Low
FAS										
4	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	51/87 (58.6%)	118/128 1 (9.2%	<b>OR 12.75</b> (7.82 to 20.78)	<b>472 more per</b> <b>1,000</b> (from 350 more to 586 more)	⊕⊕⊖⊖ Low
RND/Oth	ers		<u> </u>							
6	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	42/289 (14.5%)	122/137 4 (8.9%)	<b>OR 1.31</b> (0.55 to 3.15)	<b>24 more per</b> <b>1,000</b> (from 38 fewer to 146 more)	⊕⊕⊖⊖ Low

FASD										
5	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	188	264	-	MD 1.3 lower (2.08 lower to 0.52 lower)	⊕⊕⊖⊖ Low
AS			-							
5	serious <sup>a</sup>	serious <sup>b</sup>	serious <sup>c</sup>	not serious	none	272	601	-	MD 2.15 lower (2.73 lower to 1.57 lower)	⊕○○○ Very low
FAS										
4	serious <sup>a</sup>	serious <sup>b</sup>	serious <sup>c</sup>	not serious	none	124	374	-	MD 1.43 lower (1.88 lower to 0.97 lower)	⊕○○○ Very low
RND/Oth	hers									
2	serious <sup>a</sup>	serious <sup>b</sup>	serious <sup>c</sup>	serious <sup>d,f</sup>	none	76	139	-	MD 0.27 lower (0.86 lower to 0.31 higher)	⊕○○○ Very low
alpebral	Fissure Len	gth (Centiles)								
ASD										
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	6	71	-	MD 15.90 lower (31.41 lower to 0.21 higher)	⊕○○○ Very low
AS	•		•			4				
5	serious <sup>a</sup>	not serious	not serious	not serious	none	124	2286	-	MD 19.31 lower (21.30 lower to 17.33 lower)	⊕⊕⊕⊖ Moderate
FAS										
6	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	210	2318	-	MD 19.06 lower (27.08 lower to 11.03 lower)	⊕⊕⊖⊖ Low
RND/Oth	hers									
5	serious <sup>a</sup>	not serious	not serious	serious <sup>d</sup>	none	169	2286	-	MD 0.84 lower (4.44 lower to 2.76 higher)	⊕⊕⊖⊖ Low
alpebral	Fissure Len	gth (z-scores)	•				• •			
AS										
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	41	31	-	MD 1.37 lower (2.02 lower to 0.72 lower)	⊕⊕⊖⊖ Low
FAS	•		•			-			• • •	
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	79	47	-	MD 0.98 lower (2.27 lower to 0.31 higher)	⊕○○○ Very low
RND/Oth	hers	-	-			-	-			
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	24	16	-	MD 1.10 lower (1.69 lower to 0.51 lower)	⊕⊕⊖⊖ Low

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

**Explanations:** a) >50% of studies were rated as moderate or high risk of bias; b) High overall 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.

# Meta-analyses for 3 sentinel facial features

# Exposure studies PHILTRUM OUTCOMES

	Moderate	PAE	Contr	ol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Bandoli et al 2020*	9	45	18	253	100.0%	3.26 [1.36, 7.82]			•
Total (95% CI)		45		253	100.0%	3.26 [1.36, 7.82]		•	
Total events	9		18						
Heterogeneity: Not ap	plicable						0.01		100
Test for overall effect:	Z = 2.65 (P	= 0.008	)				0.01	Control Moderate PA	

### Very Heavy PAE and Philtrum Smoothness (3+) (1 study)

	Very Heav	y PAE	Cont	rol		Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Bandoli et al 2020*	6	19	18	253	100.0%	6.03 [2.05, 17.74]	
Total (95% CI)		19		253	100.0%	6.03 [2.05, 17.74]	◆
Total events	6		18				
Heterogeneity: Not ap	oplicable						
Test for overall effect	: Z = 3.26 (P =	= 0.001)					Control Very Heavy PAE
Dist. of his site and							

Risk of bias legend (A) RoB

## Confirmed PAE Level Unquantifiable and Philtrum Smoothness (4+) (3 studies)

	Confirmed Unquan	tifiable	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Graham et al 2013	50	110	11	102	28.6%	6.89 [3.32, 14.30]		•
Mattson et al 2010	14	38	3	60	8.6%	11.08 [2.92, 42.12]	<b>_</b>	•
Mattson et al 2013	110	196	29	154	62.8%	5.51 [3.37, 9.02]	•	•
Total (95% CI)		344		316	100.0%	6.24 [4.22, 9.22]	•	
Total events	174		43					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	= 0.00; Chi² = 1.03, df : Z = 9.19 (P ≤ 0.0000		.60); I² =	0%			0.001 0.1 1 10 1 Control Confirmed Ur	000 nquantifiable

Risk of bias legend (A) RoB

*Notes:* All unmarked studies used an Astley Lip/Philtrum Guide, \* indicates use of the criteria other than Astley Lip/Philtrum Guide. Bandoli et al 2020 used the Revised Institute of Medicine Lip/Philtrum Guide. Bandoli et al 2020 reports multiple trajectories, used Trajectory D (96.05g/week) for moderate and E (313g/week) for very heavy.

# Philtrum Rank (1-5) (m/SD)

	Confirmed	Unquantif	ïable	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
Gautam et al 2015	3.6	0.8	65	3	0.9	55	100.0%	0.70 [0.33, 1.07]		•
Total (95% CI)			65			55	100.0%	0.70 [0.33, 1.07]	•	
Heterogeneity: Not ap Test for overall effect:		0.0002)						H	4 -2 0 2 Control Confirmed Un	4 quantifiable

Risk of bias legend (A) RoB

# Philtrum Length (mm) (m/SD)

				Hea	ivy P	AE an	d Philtru	ım Length (1 study)		
	Hea	avy PA	E	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
Autti-Rämö et al 1992	14.62	0.36	16	14.12	0.37	48	100.0%	1.34 [0.73, 1.96]		•
Total (95% CI)			16			48	100.0%	1.34 [0.73, 1.96]	•	
Heterogeneity: Not appl	icable							Ļ.	<u> </u>	
Test for overall effect: Z	= 4.28 (F	° < 0.0	001)					-4	Control Heavy PAE	4
Risk of bias legend										

(A) RoB

*Notes:* Autti-Rämo et al 1992a reports drinking at the 1<sup>st</sup>, 1<sup>st</sup>-2<sup>nd</sup> and 1<sup>st</sup>-3<sup>rd</sup> trimester. Used 1<sup>st</sup> trimester only exposure for analysis.

				I	Long Pł	niltrum (%)			
			Mode	erate P	AE and	Long Philtrum (1	study)		
	Moderate	PAE	Contr	ol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Bandoli et al 2020*	7	45	20	253	100.0%	2.15 [0.85, 5.42]			•
Total (95% CI)		45		253	100.0%	2.15 [0.85, 5.42]			
Total events	7		20						
Heterogeneity: Not ap	plicable						0.1 0.2	0.5 1 2 5	10
Test for overall effect:	Z=1.62 (P	= 0.11)					0.1 0.2	Control Moderate PAE	10
<u>Risk of bias legend</u> (A) RoB									
			Very H	leavy	PAE and	Long Philtrum (1	study)		
	Very Heav	y PAE	Cont	-		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% Cl	Α
Bandoli et al 2020*	3	19	20	253	100.0%	2.18 [0.59, 8.14]			- 😑
Total (95% CI)		19		253	100.0%	2.18 [0.59, 8.14]			-
Total events	3		20						
Heterogeneity: Not ap	plicable						0.1 0.2		10
Test for overall effect:	Z = 1.16 (P	= 0.24)					0.1 0.2	Control Very Heavy PA	

Risk of bias legend (A) RoB

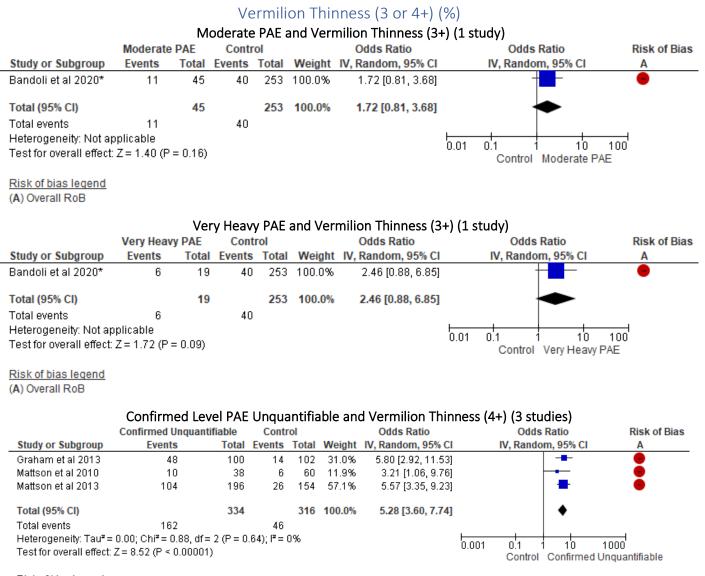
Notes: Bandoli et al 2020 reports five Trajectories, used Trajectory D (96.05g/week) for moderate and Trajectory E (313g/week) for very heavy PAE.

# Hypoplastic philtrum

# Any PAE and Hypoplastic Philtrum (%) (1 study)

	Any P	AE	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Golden et al 1982	5	12	0	12	100.0%	18.33 [0.88, 380.70]			- •
Total (95% CI)		12		12	100.0%	18.33 [0.88, 380.70]			
Total events	5		0						
Heterogeneity: Not ap	plicable						0.002		500
Test for overall effect:	Z=1.88 (	(P = 0.0	16)				0.002	Control Any PAE	000
<u>Risk of bias legend</u> ( <b>A</b> ) RoB									

Notes: PAE could not be quantified. Defined as alcohol abuse in text and Hypoplastic Philtrum defined by Jones et al 1973.



Risk of bias legend (A) Overall RoB

*Notes:* All unmarked studies used an Astley Lip/Philtrum Guide, \* indicates use of the criteria other than Astley Lip/Philtrum Guide. Bandoli et al 2020 used the Revised Institute of Medicine Lip/Philtrum Guide. Bandoli et al 2020 reports multiple trajectories, used Trajectory D (96.05g/week) for moderate and E (313g/week) for very heavy.

# Vermilion Rank (1-5) (m/SD)

	C	Confirmed	Lev	el PA	E Ur	nquar	tifiable	and Vermilion Ra	nk (1 study)	
	Confirmed	Unquantifiabl	le	Co	ontro	I		Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD T	<b>Fotal</b>	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Gautam et al 2015	3.6	0.7	65	3.2	0.7	56	100.0%	0.57 [0.20, 0.93]		•
Total (95% CI)			65			56	100.0%	0.57 [0.20, 0.93]	◆	
Heterogeneity: Not ap									-4 -2 0 2	4
Test for overall effect:	Z = 3.05 (P =	0.002)							Control Confirmed Un	quantifiable

# Frequency of Thin Upper Lip (no assessment tools reported) (%)

Ratio         Odds Ratio         Risk of Bias           Iom, 95% CI         IV, Random, 95% CI         A           1.37, 91.14]
1.37, 91.14] 😑
1.37, 91.14]
0.01 0.1 1 10 100 Contol Heavy PAE

(A) Overall RoB

Notes: Thin Upper Lip defined by Jones et al 1988

	Conf	irmed	Unquar	ntifiak	ole PAE	and thin upper li	ip (1 study)
	Confirmed Unquant	ifiable	Contr	ol		Odds Ratio	Odds Ratio Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Golden et al 1982	3	12	0	12	100.0%	9.21 [0.42, 200.59]	
Total (95% CI)		12		12	100.0%	9.21 [0.42, 200.59]	
Total events	3		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.41 (P = 0.16)						0.005 0.1 1 10 200 Control Confirmed Unquantifiable
Risk of bias legend							

(A) Overall RoB

Notes: Thin Upper Lip defined by Jones et al 1973.

#### PALPEBRAL FISSURE MEASURES

## Frequency of Short Palpebral Fissures (<3rd or <10th percentile) Moderate PAE and Short PEL <10<sup>th</sup> (%) (1 study)

	Moderate	PAE	Contr	rol		Odds Ratio	Odds Ratio Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Bandoli et al 2020	14	45	13	253	100.0%	8.34 [3.59, 19.36]	
Total (95% CI)		45		253	100.0%	8.34 [3.59, 19.36]	•
Total events	14		13				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 4.93 (P	< 0.000	01)				0.01 0.1 1 10 100 Control Moderate PAE

Risk of bias legend (A) Overall RoB

# Heavy PAE and Short PFL <3<sup>rd</sup> (%) (1 study)

						,,
Heavy I	PAE	Cont	rol		Odds Ratio	Odds Ratio Risk of Bias
Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
6	52	0	48	100.0%	13.56 [0.74, 247.52]	
	52		48	100.0%	13.56 [0.74, 247.52]	
6		0				
able						
1.76 (P =	0.08)					Control Heavy PAE
	Events 6 6 able	6 52 <b>52</b> 6	Events Total Events 6 52 0 52 6 0 cable	Events Total Events Total 6 52 0 48 52 48 6 0 cable	Events         Total         Events         Total         Weight           6         52         0         48         100.0%           52         48         100.0%         6         0           6         0         0         0         0	Events         Total         Events         Total         Weight         IV, Random, 95% CI           6         52         0         48         100.0%         13.56 [0.74, 247.52]           52         48         100.0%         13.56 [0.74, 247.52]           6         0           cable

#### Risk of bias legend

(A) Overall RoB

#### Confirmed Level PAE Unquantifiable and Short PFL <10th (%) (4 studies)

	Confirmed Unquar	tifiable	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Golden et al 1982#	2	12	0	12	3.8%	5.95 [0.26, 138.25]			•
Graham et al 2013	32	110	4	102	24.1%	10.05 [3.41, 29.63]			•
Lebel et al 2012	30	65	1	56	8.6%	47.14 [6.15, 361.45]			- 😑
Mattson et al 2010	7	38	4	60	18.2%	3.16 [0.86, 11.65]		+	•
Mattson et al 2013	85	196	13	185	45.2%	10.13 [5.39, 19.03]		-	•
Total (95% CI)		421		415	100.0%	9.15 [4.87, 17.19]		•	
Total events	156		22						
Heterogeneity: Tau <sup>2</sup> =	= 0.13; Chi <sup>2</sup> = 5.24, df	= 4 (P = 0	.26); I <sup>z</sup> =	24%					
Test for overall effect							0.001	0.1 1 10 1 Control Confirmed U	000 nquantifiable

Risk of bias legend (A) Overall RoB

*Notes:* Unmarked studies do not report norms. All studies define short PFL <10<sup>th</sup> percentile, except Golden et al 1982#, which has unclear definition of short PFL. ^ indicates use of Jones et al 1988 norms. Bandoli et al 2020 Reports multiple trajectories, Trajectory D (96.05g/week) for moderate and Trajectory E (313g/week) for very heavy.

# Palpebral Fissure Length (mm) (m/SD)

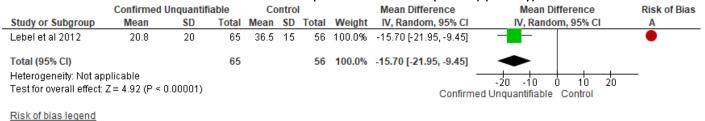
			Г	aipe	EDIA		Sure	e Len	gui (iiiii) (iii/	JUJ		
				ŀ	leavy	/ PA	E and	d PFL	(mm) (1 study)			
	Hea	avy PAE	E	0	Contro	I			Mean Difference		Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Tot	al W	/eight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Autti-Rämö et al 1992^	21.84	0.26	16	21.73	0.14	4	18 10	)0.0%	0.11 [-0.02, 0.24]			•
											Т	
Total (95% CI)			16			4	18 10	00.0%	0.11 [-0.02, 0.24]		•	
Heterogeneity: Not app	licable									-4		
Test for overall effect: 2	Z = 1.62 (P	= 0.11)	)							-4	Heavy PAE Control	4
Risk of bias legend												
(A) Overall RoB												
		~	<b>c</b> .							\ /A		
					vel P	AE U	Jnqu	antifi	able and PFL (m		••	
	Confirmed					ntrol			Mean Difference		Mean Difference	Risk of Bias
Study or Subgroup	Mean	SE	D T	otal I	Mean	SD	Total	Weigh	nt IV, Random, 95%	CI	IV, Random, 95% CI	Α
Gautam et al 2015	24.2	2.1	1	67	25.6	1.3	58	100.09	% -1.40 [-2.00, -0.8	0]		•
-											•	
Total (95% CI)				67			58	100.0	% -1.40 [-2.00, -0.8	0]	-	
Heterogeneity: Not appl										-4	-2 0 2	4
Test for overall effect: Z	= 4.54 (P <	0.0000	01)						Conf	irmed l	Jnguantifiable Control	
											-	

Risk of bias legend (A) Overall RoB

Notes: Autti-Rämo et al 1992a reports drinking at the 1st, 1st-2nd and 1st-3rd trimester. Used 1st trimester only exposure for analysis.

# Palpebral Fissure Length (centile) (m/SD)

Confirmed Level PAE Unguantifiable and PFL (centile) (1 study)



(A) Overall RoB

# Diagnosed studies

PHILTRUM MEASURES

# Frequency of Smooth Philtrum (Philtrum Smoothness 4+) (%)

			FASD	and P	hiltrum	Smoothness (4+) (6	5 studies)	
	FAS	D	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
de Water et al 2021^	15	41	3	43	16.6%	7.69 [2.03, 29.21]	_ <b></b>	•
Kalberg et al 2013	48	61	18	52	20.8%	6.97 [3.02, 16.12]		•
May et al 2006	20	22	7	67	14.1%	85.71 [16.45, 446.73]	<b>_</b>	•
Popova et al 2019	5	21	14	83	18.1%	1.54 [0.48, 4.90]		•
May et al 2021*	3	6	18	71	13.9%	2.94 [0.54, 15.91]	+	•
Roediger et al 2021	15	40	3	39	16.6%	7.20 [1.88, 27.51]		•
Total (95% CI)		191		355	100.0%	6.86 [2.67, 17.62]	•	
Total events	106		63					
Heterogeneity: Tau² = 0	).93; Chi <sup>z</sup>	²= 16.2	6, df = 5 (	(P = 0.0	06); <b>i²</b> = 6	69%		ł
Test for overall effect: Z	(= 4.00 (F	P < 0.00	001)				Control FASD	

Risk of bias legend

(A) RoB

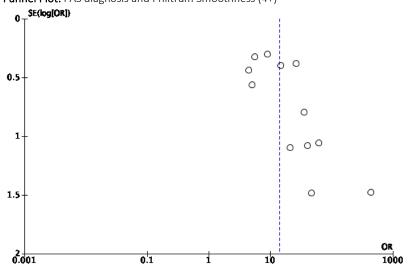
## FAS and Philtrum Smoothness (4+) (12 studies)

	FAS		Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Suttie et al 2013	20	22	15	69	7.0%	36.00 [7.55, 171.67]		?
Chambers et al 2019^	5	5	145	761	3.0%	46.61 [2.56, 847.65]		•
Mattson et al 2010	34	41	0	46	3.0%	427.80 [23.62, 7746.88]		•
Mattson et al 2013	68	79	29	154	12.4%	26.65 [12.53, 56.65]		•
May et al 2007	48	55	88	145	11.6%	4.44 [1.88, 10.50]		•
May et al 2013a	55	68	20	90	12.1%	14.81 [6.77, 32.38]		•
May et al 2015	6	7	42	190	4.7%	21.14 [2.48, 180.52]		•
May et al 2017	99	129	28	104	13.5%	8.96 [4.94, 16.25]		•
May et al 2020b^	7	8	61	413	4.8%	40.39 [4.88, 334.13]		•
May et al 2020c*	10	11	73	521	4.9%	61.37 [7.74, 486.57]		•
Suttie et al 2018	12	22	9	47	9.7%	5.07 [1.67, 15.37]		•
Viljoen et al 2005	39	64	32	146	13.2%	5.56 [2.94, 10.51]	-	•
Total (95% CI)		511		2686	100.0%	14.26 [8.21, 24.79]	•	
Total events	403		542					
Heterogeneity: Tau <sup>2</sup> = 0.5	50; Chi <b></b> =	30.61,	df = 11 (i	P = 0.0	01); I <sup>2</sup> = 6	4%		
Test for overall effect: Z =	9.42 (P <	0.000	01)				0.001 0.1 1 10 1000 Control FAS	
							Control T/10	

Risk of bias legend

(A) RoB

Funnel Plot: FAS diagnosis and Philtrum Smoothness (4+)

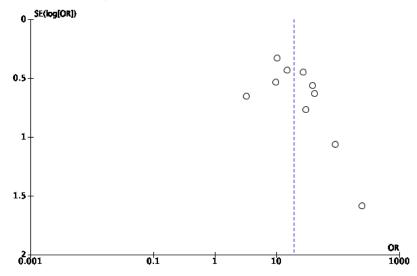


# pFAS and Philtrum Smoothness (4+) (10 studies)

	pFA	S	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	35	39	33	179	11.1%	38.71 [12.87, 116.45]		?
Suttie et al 2013	25	26	15	69	5.2%	90.00 [11.25, 719.70]		— 🥐
Astley et al 2009 (FAS/pFAS)	18	20	0	16	2.8%	244.20 [10.91, 5464.54]		<b>→                                    </b>
Chambers et al 2019^	38	44	145	761	13.1%	26.91 [11.16, 64.85]		•
May et al 2007	15	18	88	145	9.6%	3.24 [0.90, 11.69]	<b>+</b>	•
May et al 2013a	42	52	20	90	13.4%	14.70 [6.28, 34.39]		•
May et al 2015	17	19	42	190	8.0%	29.95 [6.65, 134.87]		•
May et al 2017	79	100	28	104	15.4%	10.21 [5.34, 19.51]		•
May et al 2020b^	10	16	61	413	11.5%	9.62 [3.37, 27.43]		•
May et al 2020c*	20	23	73	521	9.9%	40.91 [11.86, 141.16]		•
Total (95% CI)		357		2488	100.0%	19.22 [11.00, 33.56]	•	
Total events	299		505					
Heterogeneity: Tau <sup>2</sup> = 0.42; Chi <sup>2</sup> = 20.98, df =	= 9 (P = 0	.01); I <sup>z</sup> :	= 57%					
Test for overall effect: Z = 10.39 (P < 0.00001							0.001 0.1 1 10 10 Control pFAS	000

Risk of bias legend (A) RoB

#### Funnel Plot: pFAS diagnosis and Philtrum Smoothness (4+)



А	RND/Ot	hers a	nd Phi	ltrum	Smoo	thness (4+) (9 st	udies)	
	ARND/O	ther	Cont	rol		Odds Ratio	Odds Ratio	<b>Risk of Bias</b>
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Suttie et al 2013 (non-syndromal)	22	75	15	69	15.2%	1.49 [0.70, 3.19]		?
Astley et al 2009 (SE/AE)	6	45	0	16	2.6%	5.43 [0.29, 102.03]		•
Chambers et al 2019^ (ARND)	1	44	145	761	4.9%	0.10 [0.01, 0.72]		•
Mattson et al 2013 (non-syndromal)	42	117	29	154	18.3%	2.41 [1.39, 4.20]	-	•
May et al 2013a (ARND)	8	35	20	90	12.9%	1.04 [0.41, 2.63]		•
May et al 2017 (ARND)	10	55	28	104	14.5%	0.60 [0.27, 1.36]	-=+	•
May et al 2020b^ (ARND)	4	25	61	413	10.9%	1.10 [0.36, 3.31]	_ <b>+</b> _	•
May et al 2020c* (ARND)	3	10	73	521	8.4%	2.63 [0.67, 10.40]	+	•
Suttie et al 2018 (non-syndromal)	11	50	9	47	12.2%	1.19 [0.44, 3.20]	+	•
Total (95% CI)		456		2175	100.0%	1.22 [0.74, 2.00]	•	
Total events	107		380					
Heterogeneity: Tau <sup>2</sup> = 0.27; Chi <sup>2</sup> = 17	.00, df = 8 (	P = 0.0	3); <b>I<sup>2</sup> = 5</b> 3	3%				
Test for overall effect: Z = 0.77 (P = 0.	44)						0.001 0.1 1 10 1000 Control ARND/Others	
Risk of bias legend								
(A) RoB								

Notes: ^ indicates unclear Lip/Philtrum Guide reference and \* indicates use of the Lip/Philtrum guide other than Astley 2000.

# Philtrum (Rank 1-5) (m/SD)

			FÆ	ASD Dia	agno	osis ar	nd Philti	rum Rank (1-5) (3	studies)	
	F	ASD		Co	ontro	I		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Aragon et al 2008^	3.91	0.71	24	3.21	0.9	32	28.0%	0.70 [0.28, 1.12]		. ?
Nayak et al 2012	3.19	0.75	26	2.52	0.7	27	30.9%	0.67 [0.28, 1.06]	— <b>—</b>	•
Yang et al 2012a	3.5	0.6	58	3.2	0.8	35	41.1%	0.30 [-0.01, 0.61]		•
Total (95% CI)			108			94	100.0%	0.53 [0.26, 0.80]	•	
Heterogeneity: Tau² = Test for overall effect:					0.20)	); <b>I<sup>z</sup> =</b> 38	3%		-1 -0.5 0 0.5 1 Control FASD	_

Risk of bias legend (A) RoB

Notes: ^ indicates unclear Lip/Philtrum Guide reference. includes participants diagnosed with FAS and pFAS.

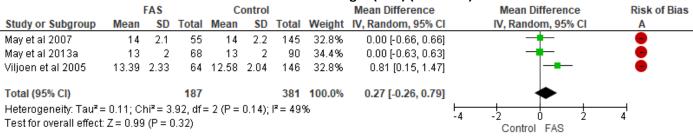
# Philtrum Length (mm) (m/SD)

				FAS	D ar	ıd Phi	ltrum Le	ength (mm) (2 stu	dies)	
	E	ASD		Co	ontro			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
May et al 2006	15	2	22	14	2	67	51.7%	1.00 [0.04, 1.96]		•
Popova et al 2019	11.7	1.8	21	12.6	4.2	83	48.3%	-0.90 [-2.09, 0.29]		•
Total (95% CI)			43			150	100.0%	0.08 [-1.78, 1.94]		
Heterogeneity: Tau² = Test for overall effect:	•			f=1(P:	= 0.01	1); I² = (	83%		-4 -2 0 2 Control FASD	

Risk of bias legend

(A) RoB

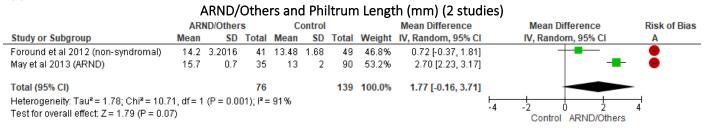
#### FAS and Philtrum Length (mm) (3 studies)



Risk of bias legend (A) RoB

#### Risk of bias legend

(A) RoB



Risk of bias legend

(A) RoB

Notes: Foround et al 2012 reported measures at 5yrs and 9yrs, used 5yrs in meta-analysis.

#### Long Philtrum (%)

Any	FASD and	d Fred	quency	/ of L	ong Ph	niltrum (4 studie	s)	
	FASD Diag	nosis	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
4.1.1 FASD								
May et al. 2006 Subtotal (95% CI)	15	22 22	27	67 <mark>67</mark>	12.4% <b>12.4%</b>	3.17 [1.14, 8.82] <b>3.17 [1.14, 8.82]</b>		- •
Total events	15		27					
Heterogeneity: Not applicable Test for overall effect: Z = 2.22 (P = 0.03)								
4.1.2 FAS								
May et al 2010 - South African Cohort (FAS/pFAS)	30	66	57	157	38.1%	1.46 [0.82, 2.62]		?
Viljoen et al. 2005	14	64	23	146		1.50 [0.71, 3.14]		•
Subtotal (95% CI)		130		303	61.7%	1.48 [0.93, 2.33]		
Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.00, df = 1 (P = Test for overall effect: Z = 1.66 (P = 0.10)	44 0.96); I² = 0%	0	80					
4.1.3 pFAS								
May et al 2010 - Italian Cohort (FAS/pFAS) Subtotal (95% CI)	21	39 <b>39</b>	61	149 <b>149</b>		1.68 [0.83, 3.42] <b>1.68 [0.83, 3.42]</b>	-	?
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.44 (P = 0.15)	21		61					
Total (95% CI)		191		519	100.0%	1.68 [1.17, 2.41]	•	
Total events	80		168					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.80, df = 3 (P = Test for overall effect: Z = 2.82 (P = 0.005) Test for subgroup differences: Chi <sup>2</sup> = 1.80, df = 2 (							0.1 0.2 0.5 1 2 5 Control FASD	10
Disk of birst is sound								

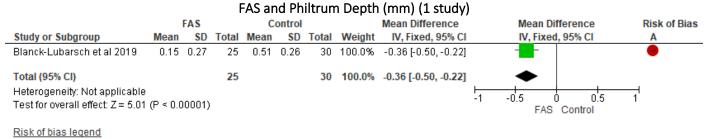
Risk of bias legend (A) RoB

*Notes:* All studies defined long philtrum as described by Hoyme 2005. May et al 2010 Italian Cohort is majority pFAS and the May et al 2010 South African Cohort is majority FAS.

# 'Other' Philtrum measures

				FAS	S and	Philtr	rum Len	gth (z-score) (1 st	udy)	
	1	FAS		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Moore et al 2002	0.73	1.5	40	0.8	0.26	31	100.0%	-0.07 [-0.54, 0.40]		•
Total (95% CI)			40			31	100.0%	-0.07 [-0.54, 0.40]		
Heterogeneity: Not ap Test for overall effect:	•		0.77)						-1 -0.5 0 0.5 Control FAS	

Risk of bias legend (A) RoB Note: Moore et al 2002 also reported pFAS.



(A) RoB

Note: Blanck-Lubarsch et al 2019b

# VERMILION MEASURES

# Frequency of Vermilion Thinness (4+) (%)

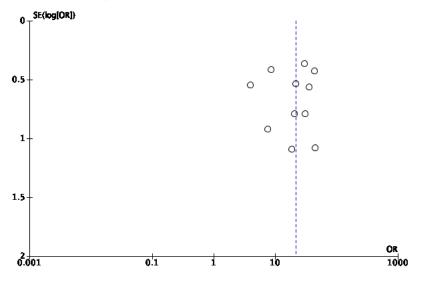
			FASE	) and \	Vermilio	n Thinness (4+) (5 s	studies)	
	FAS	D	Cont	rol		Odds Ratio	Odds Ratio Risk of Bia	as
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A	
de Water et al 2021^	10	41	3	43	20.6%	4.30 [1.09, 16.97]		
Kalberg et al 2013	43	61	3	52	21.9%	39.02 [10.75, 141.61]	👳	
May et al 2006	19	22	17	67	21.2%	18.63 [4.90, 70.87]		
May et al 2021*	4	6	18	71	15.6%	5.89 [0.99, 34.91]		
Roediger et al 2021	11	40	3	39	20.7%	4.55 [1.16, 17.86]		
Total (95% CI)		170		272	100.0%	10.10 [4.09, 24.90]	▲	
Total events	87		44					
Heterogeneity: Tau² = (	0.54; Chi <mark>²</mark>	= 8.16	, df = 4 (F	P = 0.09	l); I <sup>2</sup> = 519	6		
Test for overall effect: Z	(= 5.02 (F	P < 0.00	0001)				Control FASD	

#### Risk of bias legend

(A) Overall RoB

## FAS and Vermilion Thinness (4+) (12 studies)

	FAS		Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Suttie et al 2013	20	22	17	69	7.4%	30.59 [6.47, 144.59]		?
Chambers et al 2019^	3	5	125	761	6.3%	7.63 [1.26, 46.15]		•
Mattson et al 2010	40	41	0	46	2.7%	2511.00 [99.51, 63363.83]	— — — — — — — — — — — — — — — — — — —	→ 😑
Mattson et al 2013	71	79	26	154	11.6%	43.69 [18.79, 101.60]		•
May et al 2007	47	55	59	145	11.8%	8.56 [3.77, 19.44]		•
May et al 2013a	61	68	11	38	10.3%	21.39 [7.48, 61.15]		•
May et al 2015	6	7	46	190	5.0%	18.78 [2.20, 160.10]	— <b>—</b>	•
May et al 2017	113	129	20	104	12.4%	29.66 [14.50, 60.66]		•
May et al 2020b^	7	8	56	413	5.1%	44.63 [5.39, 369.61]		•
May et al 2020c*	9	11	93	521	7.4%	20.71 [4.40, 97.43]		•
Suttie et al 2018	12	22	11	47	10.1%	3.93 [1.34, 11.53]		•
Viljoen et al 2005	32	64	4	146	9.9%	35.50 [11.72, 107.50]		•
Total (95% CI)		511		2634	100.0%	21.72 [12.07, 39.08]	•	
Total events	421		468					
Heterogeneity: Tau <sup>2</sup> = 0.9	59; Chi <b></b> =	28.92,	df = 11 (	P = 0.0	02); <b>I<sup>z</sup> =</b> 6:	2%		<del></del>
Test for overall effect: Z =	= 10.27 (P	< 0.00					0.001 0.1 1 10 10 Control FAS	00
	,		-				CONTROL FAS	



## pFAS and Vermilion Thinness (4+) (9 studies)

	pFA	s	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Suttie et al 2013	25	26	17	69	5.3%	76.47 [9.63, 607.49]		• ?
Astley et al 2009 (FAS/pFAS)	18	20	2	16	5.2%	63.00 [7.87, 504.63]		•
Chambers et al 2019^	37	44	125	761	17.1%	26.89 [11.72, 61.69]		•
May et al 2007	15	18	59	145	10.7%	7.29 [2.02, 26.29]	_ <b></b>	•
May et al 2013a	49	52	11	38	9.9%	40.09 [10.29, 156.25]	<b>_</b>	•
May et al 2015	13	19	46	190	14.0%	6.78 [2.44, 18.86]		•
May et al 2017	80	100	20	104	19.6%	16.80 [8.42, 33.54]		•
May et al 2020b^	15	16	56	413	5.4%	95.63 [12.39, 738.18]		- 😑
May et al 2020c*	19	23	93	521	12.9%	21.86 [7.27, 65.76]		•
Total (95% CI)		318		2257	100.0%	21.08 [12.48, 35.58]	•	
Total events	271		429					
Heterogeneity: Tau <sup>2</sup> = 0.24; Ch	ni² = 13.45	, df = 8	(P = 0.10	$();  ^2 = 4$	11%			<u>,</u>
Test for overall effect: Z = 11.4	1 (P < 0.00	0001)	-				0.001 0.1 1 10 100 Control pFAS	IU

Risk of bias legend

(A) Overall RoB

## ARND/Others and Vermilion Thinness (4+) (9 studies)

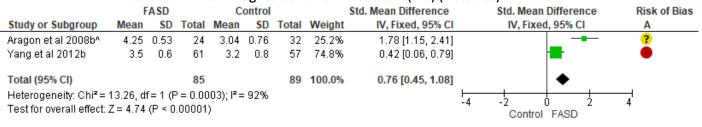
	ARND/Ot	hers	Contr	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Suttie et al 2013 (non-syndromal)	20	75	17	69	16.9%	1.11 [0.53, 2.35]	-+-	?
Astley et al 2009 (SE/ND)	3	45	2	16	2.7%	0.50 [0.08, 3.31]		•
Chambers et al 2019^ (ARND)	5	44	125	761	10.5%	0.65 [0.25, 1.69]		•
Mattson et al 2013 (non-syndromal)	33	117	26	154	27.9%	1.93 [1.08, 3.46]		•
May et al 2013a (ARND)	9	35	11	38	8.9%	0.85 [0.30, 2.39]	-+-	•
May et al 2017 (ARND)	10	55	20	104	13.4%	0.93 [0.40, 2.16]	-+-	•
May et al 2020b^ (ARND)	3	25	56	413	6.2%	0.87 [0.25, 3.00]		•
May et al 2020c* (ARND)	1	10	93	521	2.2%	0.51 [0.06, 4.09]		•
Suttie et al 2018 (non-syndromal)	14	50	11	47	11.3%	1.27 [0.51, 3.18]		•
Total (95% CI)		456		2123	100.0%	1.13 [0.83, 1.53]	•	
Total events	98		361					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 6.5	5, df = 8 (P	= 0.59)	; I² = 0%					
Test for overall effect: $Z = 0.76$ (P = 0.4	45)						0.001 0.1 1 10 10 Control ARND/Others	00

Risk of bias legend

(A) Overall RoB Notes: ^ indicates unclear Lip/Philtrum Guide reference and \* indicates use of the Lip/Philtrum guide other than Astley 2000/2001/2004.

# Vermilion Rank (1-5) (m/SD)

FASD Diagnosis and Vermilion Rank (1-5) (2 studies)



Risk of bias legend (A) Overall RoB

Notes: ^ indicates unclear Lip/Philtrum Guide reference. Aragon et al 2008b includes participants diagnosed with FAS and pFAS.

					Upp	er Lip	o Circu	larity (m/SD)	
				FA	SD an	d Upp	er Lip C	ircularity (1 stud	y)
	FASD	Diagno	sis	0	Control			Mean Difference	Mean Difference Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Nayak et al 2012	66.68	44.76	26	59.31	11.74	27	100.0%	7.37 [-10.40, 25.14]	
Total (95% CI)			26			27	100.0%	7.37 [-10.40, 25.14]	◆
Heterogeneity: Not a	oplicable								
Test for overall effect	: Z = 0.81	(P = 0	42)						Control FASD

Risk of bias legend (A) Overall RoB

Notes: Upper lip circularity as defined by Astley 2000.

#### PALPEBRAL FISSURE MEASURES

	F					bebral Fissures (		
		FASI	D and Sł	hort Pa	alpebral	Fissures (%) <3rd C	Centile (1 study)	
	FAS	D	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Popova et al 2019	10	21	9	83	100.0%	7.47 [2.49, 22.48]		•
Total (95% CI)		21		83	100.0%	7.47 [2.49, 22.48]	•	
Total events	10		9					
Heterogeneity: Not ap	oplicable							1000
Test for overall effect:	Z= 3.58 (	(P = 0.0	1003)				Control FASD	1000

Risk of bias legend

(A) Overall RoB

	FAS	5	Contr	ol		Odds Ratio	Od	ds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Rar	dom, 95% Cl	Α
May et al 2020a	1	4	14	278	16.5%	6.29 [0.61, 64.35]			•
May et al 2020b	2	8	9	413	29.7%	14.96 [2.65, 84.51]			•
May et al 2020c	4	11	28	521	53.8%	10.06 [2.78, 36.41]			•
Total (95% CI)		23		1212	100.0%	10.48 [4.08, 26.92]		•	
Total events	7		51						
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi	i <sup>z</sup> = 0.3:	5, df = 2 (	P = 0.8	4); l <sup>2</sup> = 0%	6	0.001 0.1	1 10	1000

Risk of bias legend

	pFA	S	Contr	rol		Odds Ratio		Odds	Ratio	- I	Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	I	V, Rando	m, 95% Cl		Α
May et al 2020a	7	22	14	278	34.1%	8.80 [3.09, 25.04]					•
May et al 2020b	4	16	9	413	21.7%	14.96 [4.04, 55.47]			<b>—</b>		•
May et al 2020c	9	23	28	521	44.1%	11.32 [4.51, 28.40]					•
Total (95% CI)		61		1212	100.0%	11.04 [5.99, 20.33]			•		
Total events	20		51								
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Ch	i <sup>z</sup> = 0.3	9, df = 2 (	P = 0.8	2); I <sup>z</sup> = 09	6				1000	
Test for overall effect:	Z=7.70	(P ≤ 0.0	00001)				0.001	0.1 1 Control	I 10 pFAS	1000	

Risk of bias legend

(A) Overall RoB

	ARND/	Others	s and Sł	nort Pa	alpebra	l Fissures (%) <3 <sup>rd</sup>	Centile (3 studies)	
	ARND/Ot	hers	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2020a (ARND)	0	12	14	278	25.8%	0.73 [0.04, 12.94]		•
May et al 2020b (ARND)	0	25	9	413	25.9%	0.83 [0.05, 14.75]		•
May et al 2020c (ARND)	1	10	28	521	48.3%	1.96 [0.24, 15.99]		•
Total (95% CI)		47		1212	100.0%	1.22 [0.28, 5.24]	•	
Total events	1		51					
Heterogeneity: Tau <sup>2</sup> = 0.00	); Chi <b>²</b> = 0.0	38, df =	2 (P = 0.8	83); I <b>²</b> =	0%		0.001 0.1 1 10 10	<u>_</u>
Test for overall effect: Z = (	0.26 (P = 0.	.79)					0.001 0.1 1 10 100 Control ARND/Others	00

Risk of bias legend (A) Overall RoB

Notes: May et al 2020a, May et al 2020b and May et al 2020c do not clearly reference norms used.

# Frequency of Short Palpebral Fissures (%) <10<sup>th</sup> Centile

	FAS	D	Conti	ol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Roediger et al 2021*	1	40	3	39	100.0%	0.31 [0.03, 3.09]			-
Total (95% CI)		40		39	100.0%	0.31 [0.03, 3.09]			
Total events	1		3						
Heterogeneity: Not app	licable						0.001		1000
Test for overall effect: Z	:= 1.00 (P	= 0.32	)				0.001	Control FASD	1000

Risk of bias legend (A) Overall RoB

# FAS and Short Palpebral Fissures (%) <10<sup>th</sup> Centile (7 studies)

	FAS	5	Contr	ol		Odds Ratio	Odds	Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Randoi	m, 95% Cl	Α
Suttie et al 2013#	18	22	8	69	15.3%	34.31 [9.26, 127.21]			?
Mattson et al 2010	35	41	0	46	3.1%	507.92 [27.69, 9318.45]			+ 😑
Mattson et al 2013	61	79	12	185	42.4%	48.86 [22.25, 107.28]			•
May et al 2020a	3	4	25	278	5.0%	30.36 [3.04, 302.87]			•
May et al 2020b	6	8	29	413	9.7%	39.72 [7.67, 205.65]			•
May et al 2020c	8	11	56	521	14.3%	22.14 [5.71, 85.89]			•
Suttie et al 2018	19	22	4	47	10.4%	68.08 [13.87, 334.31]			•
Total (95% CI)		187		1559	100.0%	44.05 [26.40, 73.50]		•	
Total events	150		134						
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Ch	i <sup>z</sup> = 4.3	1,df=6(	P = 0.6	3); I <sup>z</sup> = 09	6		10 100	<u>_</u>
Test for overall effect:	Z=14.49	9 (P < 0	.00001)				0.001 0.1 1 Control	10 100 FAS	10

Risk of bias legend

(A) Overall RoB

	pFA	s	Conti	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
Suttie et al 2013#	18	26	8	69	19.3%	17.16 [5.64, 52.17]		- ?
May et al 2020a	12	22	25	278	27.4%	12.14 [4.77, 30.91]		•
May et al 2020b	8	16	29	413	21.7%	13.24 [4.63, 37.85]		•
May et al 2020c	13	23	56	521	31.6%	10.79 [4.52, 25.76]		•
Total (95% CI)		87		1281	100.0%	12.75 [7.82, 20.78]	•	
Total events	51		118					
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi	<sup>2</sup> = 0.43	3. df = 3 (	P = 0.9	3); <b>I<sup>2</sup> = 0%</b>			1000

#### Risk of bias legend

(A) Overall RoB

## ARND/Others and Short Palpebral Fissures (%) <10<sup>th</sup> Centile (6 studies)

	ARND/Ot	hers	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Mattson et al 2013 (non-syndromal)	24	117	0	46	8.3%	24.37 [1.45, 409.63]		•
May et al 2020a (ARND)	0	12	25	278	8.2%	0.40 [0.02, 6.91]		•
May et al 2020b (ARND)	0	25	29	413	8.3%	0.26 [0.02, 4.30]		•
May et al 2020c (ARND)	1	10	56	521	13.8%	0.92 [0.11, 7.42]		•
Suttie et al 2013# (non-syndromal)	9	75	8	69	34.3%	1.04 [0.38, 2.87]		?
Suttie et al 2018 (non-syndromal)	8	50	4	47	27.1%	2.05 [0.57, 7.32]	+	•
Total (95% CI)		289		1374	100.0%	1.31 [0.55, 3.15]	•	
Total events	42		122					
Heterogeneity: Tau <sup>2</sup> = 0.31; Chi <sup>2</sup> = 6.86	6, df = 5 (P	= 0.23);	; l² = 27%					ł
Test for overall effect: Z = 0.61 (P = 0.5	4)						0.001 0.1 1 10 1000 Control ARND/Others	

#### Risk of bias legend (A) Overall RoB

Notes: # denotes use of Thomas 1987 norms and \* denotes Stromland et al 1999 norms. All unmarked studies did not directly reference norms used to determined short PFL.

# Palpebral Fissure Length (mm) (m/SD)

				FASD	and	Palpe	bral Fis	sure Length (5 stu	idies)	
	F	ASD		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Kalberg et al 2013	22.5	2.1	61	25.4	1.8	52	19.9%	-2.90 [-3.62, -2.18]		•
May et al 2006	24	1	22	25	1	67	22.0%	-1.00 [-1.48, -0.52]		•
Nayak et al 2012	22.36	1.43	26	22.86	1.37	27	19.6%	-0.50 [-1.25, 0.25]		•
Popova et al 2019	24	1.5	21	25.1	1.8	83	19.7%	-1.10 [-1.85, -0.35]		•
Yang et al 2012a	25	3	58	26	1	35	18.8%	-1.00 [-1.84, -0.16]		•
Total (95% CI)			188			264	100.0%	-1.30 [-2.08, -0.52]	•	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				f= 4 (P	< 0.001	01); I² =	: 84%		-4 -2 0 2 FASD Control	4

#### Risk of bias legend (A) Overall RoB

FAS and Palpebral Fissure Length (5 studies)

				o una	1 41	pebru	113541	e rengin (5 staan		
	1	FAS		Co	ontro			Mean Difference	Mean Difference	Risk of Bia
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Blanck-Lubarsch et al 2019	21.7	1.5	78	24	1.6	30	18.4%	-2.30 [-2.96, -1.64]		•
May et al 2007	23	1.1	55	25	1.2	145	22.3%	-2.00 [-2.35, -1.65]	-	•
May et al 2013a	23.1	2	68	24.5	1	90	20.3%	-1.40 [-1.92, -0.88]		•
May et al 2015	23	1	7	25	1.1	190	17.1%	-2.00 [-2.76, -1.24]	_ <b>-</b> -	•
Viljoen et al 2005	23	1.3	64	26	1.4	146	21.9%	-3.00 [-3.39, -2.61]	-	•
Total (95% CI)			272			601	100.0%	-2.15 [-2.73, -1.57]	•	
Heterogeneity: Tau <sup>2</sup> = 0.36; C	hi <b>²</b> = 26.	78, d	f= 4 (P	< 0.000	l1); I²	= 85%				<del></del>
Test for overall effect: Z = 7.30									-4 -2 U 2 FAS Control	4

#### pFAS and Palpebral Fissure Length (4 studies)

		P						,	
	<b>FAS</b>		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
23.41	0.71	35	25.03	0.36	49	29.4%	-1.62 [-1.88, -1.36]	+	•
23	0.9	18	25	1.2	145	24.3%	-2.00 [-2.46, -1.54]		•
23.5	1	52	24.5	1	90	27.4%	-1.00 [-1.34, -0.66]		•
24	1.4	19	25	1.1	90	19.0%	-1.00 [-1.67, -0.33]		•
		124			374	100.0%	-1.43 [-1.88, -0.97]	•	
<sup>2</sup> = 15.60	, df = 3	8 (P = 0	.001); I <sup>z</sup>	= 81%	6				
P ≺ 0.00I	001)							pFAS Control	4
	Mean 23.41 23 23.5 24 24 24	23.41 0.71 23 0.9 23.5 1 24 1.4	pFAS           Mean         SD         Total           23.41         0.71         35           23         0.9         18           23.5         1         52           24         1.4         19           124           * = 15.60, df = 3 (P = 0	pFAS         C           Mean         SD         Total         Mean           23.41         0.71         35         25.03           23         0.9         18         25           23.5         1         52         24.5           24         1.4         19         25           ILL           * 15.60, df = 3 (P = 0.001); P	pFAS         Control           Mean         SD         Total         Mean         SD           23.41         0.71         35         25.03         0.36           23         0.9         18         25         1.2           23.5         1         52         24.5         1           24         1.4         19         25         1.1           124           124	PFAS         Control           Mean         SD         Total         Mean         SD         Total           23.41         0.71         35         25.03         0.36         49           23         0.9         18         25         1.2         145           23.5         1         52         24.5         1         90           24         1.4         19         25         1.1         90           124         Total           ***********************************	pFAS         Control           Mean         SD         Total         Mean         SD         Total         Weight           23.41         0.71         35         25.03         0.36         49         29.4%           23         0.9         18         25         1.2         145         24.3%           23.5         1         52         24.5         1         90         27.4%           24         1.4         19         25         1.1         90         19.0%           124         25         1.1         90         19.0%           1560, df = 3 (P = 0.001); I <sup>a</sup> = 81%	PFAS         Control         Mean Difference           Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI           23.41         0.71         35         25.03         0.36         49         29.4%         -1.62 [-1.88, -1.36]           23         0.9         18         25         1.2         145         24.3%         -2.00 [-2.46, -1.54]           23.5         1         52         24.5         1         90         27.4%         -1.00 [-1.34, -0.66]           24         1.4         19         25         1.1         90         19.0%         -1.00 [-1.67, -0.33]           124         374         100.0%         -1.43 [-1.88, -0.97]	Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI           23.41         0.71         35         25.03         0.36         49         29.4%         -1.62 [-1.88, -1.36]

#### Risk of bias legend

(A) Overall RoB

#### ARND/Others and Palpebral Fissure Length (2 studies)

	ARN	D/Othe	rs	С	ontrol			Mean Difference	Mean Difference	<b>Risk of Bias</b>
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Foroud et al 2012 (non-syndromal)	25.03	0.47	41	25.03	0.36	49	54.4%	0.00 [-0.18, 0.18]	<b>+</b>	•
May et al 2013 (ARND)	23.9	1	35	24.5	1	90	45.6%	-0.60 [-0.99, -0.21]		•
Total (95% CI)			76			139	100.0%	-0.27 [-0.86, 0.31]	•	
Heterogeneity: $Tau^2 = 0.16$ ; $Chi^2 = 7.9$	•	(P = 0	.006);	<b>°</b> = 87%	)				-2 -1 0 1 2	_
Test for overall effect: Z = 0.92 (P = 0	.30)								Control ARND/Others	

#### Risk of bias legend

(A) Overall RoB

*Notes*: Foround et al 2012 reports data at 5yrs and 9yrs, used 5yrs for meta-analysis. Blanck-Lubarsch et al 2019a and Popova et al 2019 reports left and right PFL, used right PFL.

# Palpebral Fissure Length (Centiles)

			FASE	) and F	Palpe	ebral F	issure L	ength (Centiles) (1	study)	
	F	ASD		Co	ontro	I		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2021	21.8	18.7	6	37.4	22	71	100.0%	-15.60 [-31.41, 0.21]		•
Total (95% CI)			6			71	100.0%	-15.60 [-31.41, 0.21]	•	
Heterogeneity: Not a) Test for overall effect	•		0.05)						-50 -25 0 25 50 FASD Control	_

#### Risk of bias legend

(A) Overall RoB

#### FAS and Palpebral Fissure Length (Centiles) (5 studies)

		FAS		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019	7.2	5.5	5	26.9	15.7	761	16.1%	-19.70 [-24.65, -14.75]		•
Hasken et al 2021	5.8	8.4	96	24.5	15.5	313	68.4%	-18.70 [-21.10, -16.30]		•
May et al 2020a	9.8	13.6	4	30.6	16.3	278	2.2%	-20.80 [-34.26, -7.34]		•
May et al 2020b	8.6	9.9	8	32.7	15.3	413	8.0%	-24.10 [-31.12, -17.08]	- <b>-</b> -	•
May et al 2020c	10.9	14.4	11	29.1	16	521	5.3%	-18.20 [-26.82, -9.58]		•
Total (95% CI)			124			2286	100.0%	-19.31 [-21.30, -17.33]	•	
Heterogeneity: Tau <sup>2</sup> = 0	).00; Chi <sup>a</sup>	<sup>2</sup> = 2.1	7, df = 4	4 (P = 0.	70); l²	= 0%				
Test for overall effect: Z	•		•	,					-50 -25 0 25 FAS Control	50

#### Risk of bias legend

(A) Overall RoB

#### pFAS and Palpebral Fissure Length (Centiles) (6 studies)

		pFAS		0	Control			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Aragon et al 2008b (FAS/pFAS)	12.5	13.67	24	62.69	23.69	32	14.7%	-50.19 [-60.05, -40.33] 👎	_	?
Chambers et al 2019	14.6	12.8	44	26.9	15.7	761	18.1%	-12.30 [-16.24, -8.36]		•
Hasken et al 2021	15.1	15.8	81	24.5	15.5	313	18.1%	-9.40 [-13.25, -5.55]		•
May et al 2020a	14.2	15.8	22	30.6	16.3	278	16.6%	-16.40 [-23.27, -9.53]		•
May et al 2020b	18.8	19.1	16	32.7	15.3	413	15.0%	-13.90 [-23.37, -4.43]	_ <b></b>	•
May et al 2020c	12.2	12.5	23	29	16	521	17.5%	-16.80 [-22.09, -11.51]		•
Total (95% CI)			210			2318	100.0%	-19.06 [-27.08, -11.03]	•	
Heterogeneity: Tau <sup>2</sup> = 88.58; Chi	<sup>2</sup> = 59.29	H-	50 -25 0 25	50						
Test for overall effect: Z = 4.65 (P	< 0.000	D1)							pFAS Control	50

	ARN	D/Othe	rs	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
hambers et al 2019 (ARND)	29.9	14.8	44	26.9	15.7	761	24.6%	3.00 [-1.51, 7.51]		•
lasken et al 2021 (ARND)	20.9	14.7	78	24.5	15.5	313	28.2%	-3.60 [-7.29, 0.09]		•
1ay et al 2020a (ARND)	33.3	15.8	12	30.6	16.3	278	11.2%	2.70 [-6.44, 11.84]	- <b> -</b>	•
1ay et al 2020b (ARND)	33.5	13.4	25	32.7	15.3	413	20.8%	0.80 [-4.66, 6.26]		•
1ay et al 2020c (ARND)	22.3	11.5	10	29.1	16	521	15.2%	-6.80 [-14.06, 0.46]		•
otal (95% CI)			169			2286	100.0%	-0.84 [-4.44, 2.76]	•	
leterogeneity: Tau <sup>2</sup> = 8.43; Chi <sup>2</sup>	= 8.43	df = 4	(P = 0 (	18): I <b>F</b> = 1	53%				-50 -25 0 25	50

#### Risk of bias legend

(A) Overall RoB

Note: None of the papers reported norms used to determine centiles.

# Palpebral Fissure Length (z-scores)

		FAS		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
Moore et al 2002	-3.66	1.67	41	-2.29	1.15	31	100.0%	-1.37 [-2.02, -0.72]		•
Total (95% CI)			41			31	100.0%	-1.37 [-2.02, -0.72]	•	
Heterogeneity: Not ap	plicable							I		

Risk of bias legend (A) Overall RoB

# pFAS and Palpebral fissure length z-scores (2 studies)

	I	FAS		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 2009 (FAS/pFAS)	-3	0.8	20	-1.7	0.7	16	46.9%	-1.68 [-2.45, -0.90]		•
Moore et al 2002	-2.85	1.72	59	-2.29	1.15	31	53.1%	-0.36 [-0.80, 0.08]		•
Total (95% CI)			79			47	100.0%	-0.98 [-2.27, 0.31]		
Heterogeneity: Tau <sup>2</sup> = 0.77; Ch		•	(P = 0	.004); I <sup>z</sup>	= 889	Ь			-4 -2 0 2	4
Test for overall effect: Z = 1.48	(P = 0.1)	4)							pFAS Control	

Risk of bias legend

(A) Overall RoB

# ARND/Others and Palpebral fissure length z-scores (1 study)

	ARND	/Othe	rs	Co	ontro	Ľ.		Mean Difference	Mean Difference	<b>Risk of Bias</b>
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Astley et al 2009 (SE/AE)	-2.8	1.2	24	-1.7	0.7	16	100.0%	-1.10 [-1.69, -0.51]		•
Total (95% CI)			24			16	100.0%	-1.10 [-1.69, -0.51]	•	
Heterogeneity: Not applicat		0.0003							-4 -2 0 2	4

Risk of bias legend (A) Overall RoB

Notes: Astley et al 2009b does not report norms used and Moore et al 2002 use norms by Farkas 1981.

		Other Minor Facial Feature	es
Study Type	Outcome	Data	# of studies
Exposuro	Strabismus	Strabismus (%)	<b>2 studies:</b> 1 moderate PAE, 1 very heavy PAE and 1 confirmed unquantified
Exposure Studies	Interpupillary Distance	IPD (mm) (m/SD)	1 study: 1 heavy PAE
	Hypoplastic Midface	Hypoplastic Midface (%)	<b>1 study:</b> 1 moderate PAE, 1 very heavy PAE
	Ptosis	Ptosis (%)	<b>2 studies:</b> 1 moderate, 1 very heavy PAE and 1 confirmed unquantified
	Epicanthal Folds	Epicanthal Folds (%)	<b>2 studies:</b> 1 moderate PAE, 1 very heavy PAE and 1x confirmed unquantified
	Nasal Bridge	Flat Nasal Bridge (%)	0 studies
	Prognathism	Prognathism (%)	0 studies
	Innercanthal Distance	ICD (mm) (m/SD)	1 study: 1 heavy PAE
		Short ICD (%)	<b>1 study:</b> 1 moderate PAE, 1 very heavy PAE
	Anteverted Nares	Anteverted Nares (%)	<b>2 studies:</b> 1 moderate PAE, 1 very heavy PAE and 1 confirmed unquantified
	Outercanthal Distance	Outercanthal Distance (mm) (m/SD)	1 study: 1 heavy PAE
	Mandibular Arc	Mandibular Arc (mm) (m/SD)	0 studies
	Maxillary Arc	Maxillary Arc (mm) (m/SD)	0 studies
	Strabismus	Strabismus (%)	<b>7x studies:</b> 1x FASD, 5x FAS, 5x pFAS, 3x ARND/Others
Diagnosed	Interpupillary Distance	IPD (mm) (m/SD)	<b>1 study:</b> 1x FAS, 1x pFAS, and 1x ARND/Others
Studies		Short IPD (%) IPD (centile)	<ul> <li>4 studies: 3x FAS, 3x pFAS and 1x ARND/Others</li> <li>6 studies: 2x FASD, 5x FAS, 5x pFAS, and 5x ARND/Others</li> </ul>
	Hypoplastic Midface	Hypoplastic Midface (%)	<b>7 studies:</b> 1x FASD, 6x FAS, 5x pFAS, 3x ARND/Others
	Ptosis	Ptosis (%)	<b>8x studies:</b> 1x FASD, 6x FAS, 6x pFAS, 4x ARND/Others
	Epicanthal Folds	Epicanthal Folds (%)	6 studies: 2x FASD, 4x FAS, 3x pFAS, 2x ARND/Others
	Nasal Bridge	Flat Nasal Bridge (%)	<b>6 studies:</b> 1x FASD, 4x FAS, 4x pFAS
		Nasal Bridge Length (mm) (m/SD)	1 study: 1x FAS/pFAS and 1x ARND/Other
		Nasal Bridge Length (z-score)	1 study: 1x FAS and 1x pFAS
	Prognathism	Prognathism (%)	4 studies: 1x FASD, 3x FAS, 2x pFAS, 1x ARND/Others
	Innercanthal Distance	ICD (mm) (m/SD)	<b>5 studies:</b> 2x FASD, 2x FAS, 2x pFAS (1x FAS/pFAS) and 2x ARND/Others
		Short ICD (%)	<b>6 studies:</b> 2x FASD, 3x FAS, 3x pFAS and 1x ARND/Others
		ICD (centile)	2 studies: 2x FAS, 2x pFAS and 2x ARND/Others
		ICD (z-score)	1 study: 1x FAS and 1x pFAS
	Anteverted Nares	Anteverted Nares (%)	<b>6 studies:</b> 1x FASD, 4x with FAS, 4x pFAS, 2x ARND/Others
	Outercanthal Distance	Outercanthal distance (mm) (m/SD)	1 study with FAS/pFAS and ARND/Others
		Outercanthal distance (centile)	<b>5 studies</b> 2x FASD, 4x FAS, 4x pFAS and 4x ARND/Others
	Mandibular Arc	Mandibular Arc (mm) (m/SD)	<b>7 studies:</b> 1x FASD, 6x FAS, 6x pFAS, and 6x ARND/Others
		Mandibular Arc (z-score)	1 study: 1x FAS and 1x pFAS
	Maxillary Arc	Maxillary Arc (mm) (m/SD)	7 studies: 1x FASD, 6x FAS, 6xpFAS and 6x ARND/Others
		Maxillary Arc (z-score)	1 study: 1x FAS and 1x pFAS

# Summary of available outcomes for other minor facial features

# GRADE ratings for other minor facial features

		Cert	tainty assessr	nent		Nº of pa	atients	E	ffect	
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other considerati ons	PAE	Control	Relative (95% Cl)	Absolute (95% Cl)	Certainty
EXPOSUR	E STUDIE	S								
STRABISM	IUS									
STRABISM	IUS (%)									
Moderate	PAE									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	2/45	5/253	<b>OR 2.31</b> (0.43 to 12.27)	-	⊕○○○ Very Low
Very Heav	y PAE									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/19 (5.3%)	2/253 (2.0%)	<b>OR 2.76</b> (0.31 to 24.86)	<b>33 more per</b> <b>1,000</b> (from 14 fewer to 314 more)	⊕○○○ Very Low
Confirmed	d Unquar	ntifiable						•		
1	a a	not serious	not serious	very serious <sup>d,e,f</sup>	none	5/12 (41.7%)	0/12 (0.0%)	OR 18.33 (0.88 to 380.70)	-	⊕○○○ Very Low
INTERPUP	ILLARY C	DISTANCE								
Interpupil	lary Dist	ance (mm) (m/	/SD)							
Heavy PA	E									
1	serious ª	not serious	not serious	serious <sup>e, f</sup>	none	17	48	-	SMD 3.66 lower (4.51 lower to 2.81 lower)	⊕⊕⊖⊖ Low
HYPOPLAS	STIC MID	FACE					•	•		•
Hypoplast	ic Midfa	ce (%)								
Moderate	PAE									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	2/45	2/253	<b>OR 5.84</b> (0.80 to 42.55)	-	⊕○○○ Very Low
Very Hea	vy PAE									
1	a a	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/19 (5.3%)	2/253 (0.8%)	<b>OR 6.97</b> (0.60 to 80.61)	<b>45 more per</b> <b>1,000</b> (from 3 fewer to 383 more)	⊕○○○ Very Low
PTOSIS										
Ptosis (%)										
Moderate	PAE									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/45	2/253	<b>OR 2.85</b> (0.25 to 32.13)	-	⊕○○○ Very Low
Very Hea	vy PAE									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	0/19 (0.0%)	2/253 (0.8%)	<b>OR 2.58</b> (0.12 to 55.63)	<b>12 more per</b> <b>1,000</b> (from 7 fewer to 299 more)	⊕○○○ Very Low
Confirmed	d Unquar	ntifiable							,	
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/12 (8.3%)	0/12 (0.0%)	<b>OR 3.26</b> (0.12 to 88.35)	-	⊕○○○ Very Low
EPICANTH										
Epicantha	l Folds (%	%)								
Moderate	PAE									

										26
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	25/45	144/253	<b>OR 0.95</b> (0.50 to 1.79)	-	⊕○○○ Very Low
Very Heav	vy PAE							, ,		
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	11/19 (57.9%)	144/253 (56.9%)	<b>OR 1.04</b> (0.40 to 2.68)	<b>10 more per</b> <b>1,000</b> (from 223 fewer to 211 more)	⊕○○○ Very Low
Confirme	d Unqua	ntifiable								
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/12 (8.3%)	1/12 (8.3%)	<b>OR 1.00</b> (0.06 to 18.08)	-	⊕○○○ Very Low
NASAL BR	RIDGE (0	STUDIES)					-			
PROGNAT	THISM (O	STUDIES)								
INNERCA	NTHAL D	ISTANCE								
Innercant	thal dista	nce (mm) (m/s	SD)							
Heavy PA	E									
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	17	48	-	SMD 1.42 lower (2.03 lower to 0.82 lower)	⊕⊕⊖⊖ Low
Short ICD	(%)									
Moderate	e PAE					-	-			
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	12/45	18/253	<b>OR 4.75</b> (2.10 to 10.74)	-	⊕⊕⊖⊖ Low
Heavy PA	E		1			-	-			
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	7/19 (36.8%)	18/253 (7.1%)	<b>OR 7.62</b> (2.67 to 21.72)	<b>297 more per</b> <b>1,000</b> (from 99 more to 553 more)	⊕⊕⊖⊖ Low
ANTEVER	TED NAR	ES				•				1
Anteverte	ed Nares	(%)								
Moderate	e PAE									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	8/45	45/253	<b>OR 1.00</b> (0.44 to 2.29)	-	⊕○○○ Very Low
Very Heav	vy PAE		-							-
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	5/19 (26.3%)	8/45 (17.8%)	<b>OR 1.65</b> (0.57 to 4.82)	85 more per 1,000 (from 87 fewer to 383 more)	⊕○○○ Very Low
Confirme	d Unqua	ntifiable				•		•		
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	8/12 (66.7%)	0/12 (0.0%)	OR 47.22 (2.24 to 996.02)	-	⊕○○○ Very Low
OUTERCA	NTHAL C	DISTANCE								
Outercan	thal dista	ance (mm) (m/	SD)							
Heavy PA	E									
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	17	48	-	SMD 3.16 lower (3.95 lower to 2.37 lower)	⊕⊕⊖⊖ Low
MANDIBL	JLAR ARG	C (O STUDIES)								
MAXILLAI		-								
		-								
MAXILLAI DIAGNOS STRABISN	ED STUD /IUS	-								
MAXILLAI DIAGNOS	ED STUD /IUS	-								

										27
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	2/22 (9.1%)	2/67 (3.0%)	<b>OR 3.25</b> (0.43 to 24.57)	-	⊕○○○ Very Low
FAS				1 1				,		
5	serious ª	serious <sup>b</sup>	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	12/196 (6.1%)	25/1420 (1.76%)	<b>OR 6.19</b> (0.99 to 38.58)	-	⊕○○○ Very Low
pFAS										•
5	serious ª	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	none	7/175 (4%)	31/1453 (2.1%)	<b>OR 1.82</b> (0.56 to 5.95)	-	⊕○○○ Very Low
ARND/O	thers									
3	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	0/101 (0.0%)	15/1129 (1.3%)	<b>OR 0.75</b> (0.14 to 4.06)	<b>3 more per</b> <b>1,000</b> (from 24 fewer to 65 more)	⊕○○○ Very Low
INTERPU	IPILLARY [	DISTANCE								
Interpup	illary Dist	ance (mm) (m	/SD)							
FAS										
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	68	90	-	SMD 0.02 lower (0.34 lower to 0.29 higher)	⊕○○○ Very Low
pFAS			T			-	-			
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	52	90	-	SMD 0.02 lower (0.36 lower to 0.32 higher)	⊕○○○ Very Low
ARND/O	thers			11		I	1			
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	35	90	-	SMD 0.02 lower (0.41 lower to 0.37 higher)	⊕○○○ Very Low
Short IPI	D <10% (%	5)		•				•		•
FAS										
3	serious ª	serious <sup>b</sup>	serious <sup>c</sup>	serious <sup>e,f</sup>	none			<b>OR 5.98</b> (1.98 to 18.80)	-	⊕○○○ Very Low
pFAS										
3	serious ª	serious⁵	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	28/109 (25.69%)	34/414 (8.21%)	<b>OR 4.01</b> (0.23 to 70.57)	-	⊕○○○ Very Low
ARND/O	thers									•
1	serious ª	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	18/35 (51.4%)	11/90 (12.2%)	<b>OR 7.60</b> (3.05 to 18.99)	<b>392 more per</b> <b>1,000</b> (from 176 more to 603 more)	⊕○○○ Very Low
Interpup	illary Dist	ance (centile)								
FASD										
2	seriousª	not serious	not serious	not serious	none	1396	673	-	SMD 0.73 lower (0.83 lower to 0.63 lower)	⊕⊕⊕⊖ Moderate
FAS										
5	serious ª	not serious	not serious	not serious	none	608	2216	-	SMD 1.04 lower (1.15 lower to 0.92 lower)	⊕⊕⊕⊖ Moderate
pFAS										
5	serious ª	not serious	not serious	not serious	none	584	2216	-	SMD 0.50 lower (0.66 lower to 0.35 lower)	⊕⊕⊕⊖ Moderate
ARND/O	thers									

							-	-	-	
5	serious ª	not serious	not serious	serious <sup>d</sup>	none	425	2216	-	SMD 0.24 lower (0.57 lower to 0.09 higher)	⊕⊕⊖⊖ Low
HYPOPL/	ASTIC MID	FACE				<b>_</b>	<u> </u>	1	<u> </u>	<u>.</u>
Hvpopla	stic Midfa	ce (%)								
FASD										
	corious	not serious	not sorious	Voru	nono	6/22	8/67	OR 2.77	-	000
1	serious a	not senous	not serious	very serious <sup>d,e,f</sup>	none	(27.3%)	-	(0.84 to 9.13)		⊕ UOU Very Low
FAS				3011003		(27.370)	(11.570)	(0.04 (0 5.15)		1017 2011
6	serious	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	220/246	285/127	<b>OR 6.60</b> (3.64		000
0	a	3011003	not senious	3011003	none	(63.58%)	6	to 11.96)		Very Low
						(,	(22.34%)			
pFAS				•		•	•	•		•
5	serious	not serious	serious <sup>c</sup>	not serious	none	125/212	240/950	<b>OR 3.68</b> (2.51		$\oplus \oplus \bigcirc \bigcirc$
	а					-	, (25.26%)			Low
ARND/O	thers			•			•			•
3	serious	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	50/100	190/715	OR 2.58	217 more per	000
	а					(50.0%)	(26.6%)	(1.58 to 4.22)	-	Very Low
									(from 98 more	
									to 339 more)	
PTOSIS										
Ptosis (%	6)									
FASD										
1	serious	not serious	not serious	serious <sup>e,f</sup>	none	3/22	0/67	OR 24.23	-	$\oplus \oplus \bigcirc \bigcirc$
	а					(13.6%)	(0.0%)	(1.20 to		Low
								489.48)		
FAS										
6	serious	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	-	62/1659	OR 7.34	-	$\oplus OOO$
	а					(15.8%)	(3.7%)	(3.98 to		Very Low
								13.57)		
pFAS			1					1	T	
6	serious	not serious	not serious	serious <sup>f</sup>	none		68/1692		-	$\oplus \oplus \bigcirc \bigcirc$
	а					(7.8%)	(4.01%)	(1.53 to 4.71)		Low
ARND/O			<u>г .</u>	,					-	
4	serious a	not serious	not serious	very	none	5/159	59/1368		3 more per	<b>000</b>
	d			serious <sup>d,e,f</sup>		(3.1%)	(4.3%)	(0.43 to 2.69)	<b>1,000</b> (from 24 fewer to 65	Very Low
									more)	
EPICANT	HAL FOLD	S	I			<u> </u>			11012)	I
	nal Folds (9									
-	iai Polus (7	·•/								
FASD							1.5.15			
2	serious a	not serious	not serious	serious <sup>e,f</sup>	none	18/48	12/94	OR 4.61	275 more per	<b>@@</b> OO
	a					(37.5%)	(12.8%)	(1.86 to	<b>1,000</b> (from 86 more	Low
								11.41)	to 498 more)	
FAS	1 1		L	1 1		1	1	1		L
4	serious	not serious	serious <sup>c</sup>	not serious	none	116/199	170/512	OR 2.34	-	
4	a	not serious	Serious	not serious	none	-	-	(1.66 to 3.32)		⊕⊕⊖⊖ Low
pFAS			1	1		(30.2370)	.02.00/0/	(1.00 (0 0.02)	1	I
	sorious	not corious	serious <sup>c</sup>	not serious	nono	50/93	134/397	OR 2.12	-	
3	serious a	not serious	Serious	not serious	none	-	-	(1.29 to 3.47)		⊕⊕⊖⊖ Low
ARND/O			I			(33.7070)	(33.7370)	(1.23 (0 3.47)	I	1 2011
-		contac-h	not contact			20/40	62/252	00.4.00	122	
2	serious a	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	none	29/48	63/252	OR 1.86	<b>133 more per</b>	⊕○○○ Very low
	a		I	serious		(60.4%)	(25.0%)	(U.13 to 27.8)	1,000 (from 208	verylow

NASAL BR Flat Nasal FASD 1	-								fewer to 651	
lat Nasal	-								more)	
ASD	Bridge (%			<u> </u>		1		L	morey	
		%)								
1										
	serious ª	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	Not estimable	-	N/A
AS						<b>·</b> · · ·				
4	serious ª	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	94/194 (85.9%)	87/571 (15.24%)	<b>OR 3.70</b> (2.10 to 6.55)	-	⊕⊖⊖⊂ Very Low
oFAS										
4	serious ª	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	none	44/128 (34.38%)	81/604 (13.41%)	<b>OR 3.51</b> (1.17 to 10.55)	-	⊕⊖⊖⊂ Very Low
ARND/Ot	hers									
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	20/35 (57.1%)	33/90 (36.7%)	<b>OR 2.30</b> (1.04 to 5.10)	<b>204 more per</b> <b>1,000</b> (from 9 more to 380 more)	⊕○○C Very Low
Nasal Bric	lge Lengt	h (mm) (m/SD)								
AS/pFAS	5									
1	serious ª	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	35	49	-	SMD 3.29 lower (3.96 lower to 2.62 lower)	⊕⊖⊖⊂ Very Low
ARND/Ot	hers									
1	serious ª	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	41	49	-	SMD 1.69 lower (2.17 lower to 1.2 lower)	⊕⊖⊖⊂ Very Low
	lge Lengt	h (z-score)								
AS										
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	39	31	-	SMD 0.75 lower (1.24 lower to 0.26 lower)	⊕⊕⊖C Low
oFAS										
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	59	31	-	SMD 0.17 lower (0.61 lower to 0.26 higher)	⊕○○C Very Low
PROGNAT	THISM		•				•			•
Prognath	ism (%)									
ASD										
1	serious ª	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	Not estimable	-	N/A
AS			•				•			•
3	serious ª	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	12/187 (6.4%)	5/381 (1.3%)	<b>OR 4.87</b> (1.75 to 13.61)	-	⊕⊖⊖⊂ Very Low
oFAS										
2	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	3/70 (4.2%)	5/253 (1.97%)	<b>OR 2.12</b> (0.45 to 10.06)		⊕⊖⊖⊂ Very Low
ARND/Ot	hers			· I		•	-	· ·	-	-
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	1/35 (2.9%)	2/90 (2.2%)	<b>OR 1.29</b> (0.11 to 14.74)	6 more per 1,000 (from 20 fewer to 229 more)	⊕○○C Very Low
NNERCA	NTHAL D	ISTANCE							,	

Innercan	thal dista	nce (mm) (m/	SD)							
FASD			•							
2	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	47	110	-	<b>MD 0.45 higher</b> (0.41 lower to 1.30 higher)	⊕○○○ Very Low
FAS										
2	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	96	120	-	MD 1.64 lower (2.71 lower to 0.56 lower)	⊕⊕⊖⊖ Low
pFAS										
2	serious ª	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	87	139	-	MD 0.47 lower (0.73 lower to 0.22 lower)	⊕○○○ Very Low
ARND/O	thers								•	•
2	serious ª	serious <sup>b</sup>	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	76	139	-	MD 0.69 lower (2.68 lower to 1.3 higher)	⊕○○○ Very Low
Short inn	ercantha	l distance (%)								
FASD										
2	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	14/43 (32.6%)	43/150 (28.7%)	<b>OR 1.48</b> (0.62 to 3.55)	85 more per 1,000 (from 87 fewer to 301 more)	⊕○○○ Very Low
FAS									•	•
3	serious ª	not serious	serious <sup>c</sup>	serious <sup>f</sup>	none	44/185 (23.78%)	43/381 (11.29%)	<b>OR 2.33</b> (1.43 to 3.81)	-	⊕○○○ Very Low
pFAS			1				T		1	
3	serious ª	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	19/109 (17.43%)	61/414 (14.73%)	<b>OR 1.19</b> (0.48 to 2.94)	-	⊕○○○ Very Low
ARND/O				1		0 /00	10/00			
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	9/38 (23.7%)	18/90 (20.0%)	<b>OR 1.24</b> (0.50 to 3.08)	<b>37 more per</b> <b>1,000</b> (from 89 fewer to 235 more)	⊕○○○ Very Low
Innercan	thal dista	nce (centile)	•			-	•	•		•
FAS										
2	serious ª	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	592	766	-	SMD 0.76 lower (1.37 lower to 0.15 lower)	⊕○○○ Very Low
pFAS	<u> </u>						-			-
2	serious ª	not serious	not serious	serious <sup>d,e</sup>	none	502	766	-	SMD 0.26 lower (0.54 lower to 0.02 higher)	⊕⊕⊖⊖ Low
ARND/O	thers						-			-
2	serious ª	not serious	not serious	not serious	none	345	766	-	SMD 0.51 lower (0.64 lower to 0.37 lower)	⊕⊕⊕⊖ Moderate
	thal Dista	nce (z-score)								
<b>FAS</b> 1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	41	31	-	<b>SMD 0.17 lower</b> (0.76 lower to 0.41 higher)	⊕○○○ Very Low
pFAS	· · ·									
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	59	31	-	SMD 0.12 higher (0.45 lower to 0.70 higher)	⊕○○○ Very Low

	RTED NAR									
Antevert	ed Nares	(%)								
FASD										
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	8/22 (36.4%)	6/67 (9.0%)	<b>OR 5.81</b> (1.74 to 19.43)	-	⊕⊕⊖C Low
FAS	1 1			1			1	, ,	4	1
4	serious a	not serious	serious <sup>c</sup>	serious <sup>f</sup>	none	78/316	64/485	<b>OR 1.92</b> (1.07 to 3.44)	-	⊕○○○ Very Low
pFAS										
4	serious a	not serious	serious <sup>c</sup>	serious <sup>f</sup>	none	61/209	84/518	OR 2.16 (1.16 to 4.02)	-	⊕○○○ Very Low
ARND/O	thers							-		
2	serious a	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	13/90 (14.4%)	47/194 (24.2%)	<b>OR 0.51</b> (0.15 to 1.76)	-	⊕○○○ Very Low
OUTERCA	ANTHAL D	ISTANCE						•	•	
Outercar	nthal dista	nce (mm) (m/	/SD)							
FAS/pFA	s									
1	serious ª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	35	49	-	SMD 3.98 lower (4.74 lower to 3.23 lower)	⊕⊖⊖⊂ Very Low
ARND/O	thers						_			_
1	serious ª	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	41	49	-	SMD 3.88 higher (3.17 higher to 4.59 higher)	⊕⊖⊖⊂ Very Low
Outercar	nthal dista	nce (centile)				-			• •	
FASD										
2	seriousª	not serious	not serious	not serious	none	792	419	-	SMD 0.19 lower (0.31 lower to 0.06 lower)	⊕⊕⊕⊖ Moderate
FAS				•					· · · · ·	
4	serious ª	not serious	not serious	not serious	none	322	1800	-	SMD 1.33 lower (1.51 lower to 1.15 lower)	⊕⊕⊕⊖ Moderate
pFAS										
4	serious ª	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	355	1800	-	<b>SMD 0.6 lower</b> (0.87 lower to 0.33 lower)	⊕○○○ Very Low
ARND/O	thers			<u> </u>		-				
4	serious ª	serious <sup>b</sup>	not serious	serious <sup>d,e</sup>	none	289	1800	-	<b>SMD 0.2 lower</b> (0.61 lower to 0.21 higher)	⊕⊕⊖C Low
MANDIB	ULAR ARC									
Mandibu	lar Arc (m	וm) (m/SD)								
FASD										
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	6	71	-	<b>SMD 0.8 lower</b> (1.64 lower to 0.05 higher)	⊕○○○ Very Low
FAS						•		•		•
6	serious ª	not serious	not serious	serious <sup>e</sup>	none	225	2167	-	SMD 1.24 lower (1.59 lower to 0.88 lower)	⊕⊕⊖C Low

pFAS										
6	serious ª	not serious	not serious	not serious	none	257	2167	-	SMD 0.31 lower (0.49 lower to 0.13 lower)	⊕⊕⊕⊖ Moderate
ARND/O	thers									
6	serious ª	serious⁵	not serious	serious <sup>d,e</sup>	none	181	2167	-	SMD 0.23 lower (0.63 lower to 0.16 higher)	⊕○○○ Very Low
Mandibu	ular Arc (z	-score)	•	•			•			•
FAS										
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	40	31	-	SMD 1.37 lower (1.90 lower to 0.87 lower)	⊕⊕⊖⊖ Low
pFAS										
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	59	31	-	SMD 0.44 lower (1.04 lower to 0.16 higher)	⊕○○○ Very Low
MAXILLA	ARY ARC									
Maxillar	y Arc (mm	) (m/SD)								
FASD										
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	6	71	-	SMD 0.7 lower (1.54 lower to 0.14 higher)	⊕○○○ Very Low
FAS				<u> </u>			<u> </u>			
6	serious ª	not serious	not serious	serious <sup>e</sup>	none	225	2167	-	SMD 0.94 lower (1.35 lower to 0.54 lower)	⊕⊕⊖⊖ Low
pFAS				<u> </u>			<u> </u>		· · · · ·	
6	serious ª	not serious	not serious	not serious	none	257	2167	-	SMD 0.28 lower (0.47 lower to 0.10 lower)	⊕⊕⊕⊖ Moderate
ARND/O	thers			•		•			•	
6	serious ª	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	none	181	2167	-	SMD 0.15 lower (0.47 lower to 0.18 higher	⊕○○○ Very Low
Maxillar	y Arc (z-sc	ore)							•	•
FAS										
1	serious ª	not serious	not serious	serious <sup>e,f</sup>	none	40	31	-	SMD 2.05 lower (2.68 lower to 1.42 lower)	⊕⊕⊖⊖ Low
pFAS										
1	serious ª	not serious	not serious	very serious <sup>d,e,f</sup>	none	59	31	-	SMD 0.36 lower (0.95 lower to 0.24 higher)	⊕○○○ Very Low

Notes: CI: confidence interval; MD: mean difference; SMD: standard 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.

# Meta-analyses for other minor facial features

Frequency of Strabismus (%)         Moderate PAE and Frequency of Strabismus (%) (1 study)         Moderate PAE Control       Odds Ratio       Notal Events       Total Events	Exposure studies	5											
Woderate PAE and Frequency of Strabismus (%) (1 study)         Moderate PAE       Control       Odds Ratio       Odds Ratio       Risk of Bias         Bandoli et al 2020       2       45       5       253       100.0%       2.31 [0.43, 12.27]       Image: Control Cont	<u>STRABISMUS</u>												
Woderate PAE and Frequency of Strabismus (%) (1 study)         Moderate PAE       Control       Odds Ratio       Odds Ratio       Risk of Bias         Bandoli et al 2020       2       45       5       253       100.0%       2.31 [0.43, 12.27]       Image: Control Cont					Freau	lency o	of St	rabismus (%	)				
Moderate PAE Events         Control         Odds Ratio         Risk of Bias           Study or Subgroup         Events         Total         Events         Total         Weight         IV, Random, 95% Cl         IV, Random, 95% Cl         A           Bandoli et al 2020         2         45         5         253         100.0%         2.31 [0.43, 12.27]           Total         45         253         100.0%         2.31 [0.43, 12.27]           Total events         2         5           Heterogeneity, Not applicable         Test for overall effect Z = 0.98 (P = 0.33)         Events         Total         Very Heavy PAE         Control         Odds Ratio         Odds Ratio         Odds Ratio         Noderate PAE           Risk of bias leagend         (A) Overall RoB         Very Heavy PAE         Control         Odds Ratio         Odds Ratio         Odds Ratio         Odds Ratio         Noderate PAE           Study or Subgroup         Events         Total         Events         Total         Weight         IV, Random, 95% Cl         IV, Random, 95% Cl         A           Bandoli et al 2020         1         19         253         100.0%         2.76 [0.31, 24.86]         Odds Ratio         Control         Control         Very Heavy PAE <td></td> <td>М</td> <td>odera</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>·</td> <td>(vhuta</td> <td></td> <td></td>		М	odera						·	(vhuta			
Study or Subgroup         Events         Total         Events         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI         IV, Random, 95% CI         A           Bandoli et al 2020         2         45         5         253         100.0%         2.31 [0.43, 12.27]         IV, Random, 95% CI         A           Total events         2         5         5         100.0%         2.31 [0.43, 12.27]         IV						neque	•		5 (70) (1		tio	Risk of Bias	
Bandoli et al 2020       2       45       5       253       100.0%       2.31 [0.43, 12.27]         Total (95% CI)       45       253       100.0%       2.31 [0.43, 12.27]         Total events       2       5         Heterogeneity: Not applicable       2       5         Test for overall effect: Z = 0.98 (P = 0.33)       Very Heavy PAE       Trequency of Strabismus (%) (1 study)         Very Heavy PAE       Control       Odds Ratio       Odds Ratio         (A) Overall RoB       Events       Total       Events       Total         Study or Subgroup       Events       Total       Events       Total       Very Heavy PAE         Total (95% CI)       19       253       100.0%       2.76 [0.31, 24.86]       0.001       0.1       1       0.00         Total (95% CI)       19       253       100.0%       2.76 [0.31, 24.86]       0.001       0.1       1       0.001         Total (95% CI)       19       253       100.0%       18.33 [0.38, 380.70]       Control       Very Heavy PAE         Risk of bias legend (A) Overall RoB       1       5       12       0       12       100.0%       18.33 [0.38, 380.70]         Total (95% CI)       12       0       12	Study or Subgroup					Weight			ľ	V, Random,	95% CI	Α	
Total events 2 5 Heterogeneity: Not applicable Test for overall effect: Z = 0.98 (P = 0.33)		2	45	5	253	100.0%	2.	31 [0.43, 12.27]				•	
Total events 2 5 Heterogeneity: Not applicable Test for overall effect: Z = 0.98 (P = 0.33)	Total (95% CI)		45		253	100.0%	2.	31 [0.43, 12,27]					
Heterogeneity: Not applicable Test for overall effect: $Z = 0.98$ (P = 0.33) Risk of Dias legend (A) Overall RoB Very Heavy PAE and Frequency of Strabismus (%) (1 study) Very Heavy PAE Total Veight IV, Random, 95% Cl V, Random, 95% Cl A Bandoli et al 2020 1 19 253 100.0% 2.76 [0.31, 24.86] Total (95% Cl) 19 253 100.0% 2.76 [0.31, 24.86] Total events 1 5 Heterogeneity: Not applicable Test for overall effect: $Z = 0.90$ (P = 0.37) Risk of Dias legend (A) Overall RoB Risk of Dias legend (A) Overall RoB Risk of Dias legend (A) Overall RoB		2		5			_						
Test for overall effect: $Z = 0.98$ (P = 0.33) Control Moderate PAE Risk of bias legend (A) Overall RoB Very Heavy PAE Control Odds Ratio Study or Subgroup Events Total Events Total Weight IV, Random, 95% Cl IV, Random, 95% Cl A Bandoli et al 2020 1 19 253 100.0% 2.76 [0.31, 24.86] Total (95% Cl) 19 253 100.0% 2.76 [0.31, 24.86] Total events 1 5 Heterogeneity: Not applicable Test for overall effect: $Z = 0.90$ (P = 0.37) Risk of bias legend (A) Overall RoB Study or Subgroup Events Total Events Total Weight IV, Random, 95% Cl IV, Random, 95% Cl A Events Total Events Total Events Total Events Total Events Total Veight IV, Random, 95% Cl I												<del></del>	
Risk of bias legend (A) Overall RoB         Very Heavy PAE Control Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Very Heavy PAE       Control       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Very Heavy PAE       Control       Odds Ratio       Not as for the state of the state	Test for overall effect:	Z = 0.98 (P =	= 0.33)						U.U1 U.			00	
Very Heavy PAE and Frequency of Strabismus (%) (1 study)         Very Heavy PAE       Control       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Very Heavy PAE       Control       Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Very Heavy PAE       Control       Odds Ratio       Odds Ratio       Notal Study of Subgroup       Fevents       Total       Weight IV, Random, 95% CI       N, Random, 95% CI       A         Total (95% Cl)       19       253       100.0%       2.76 [0.31, 24.86]										Control M			
Very Heavy PAE and Frequency of Strabismus (%) (1 study)         Very Heavy PAE       Control       Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Events       Total       Events       Total       Weight       IV, Random, 95% CI       IV, Random, 95% CI       A         Bandoli et al 2020       1       19       5       253       100.0%       2.76 [0.31, 24.86]       IV, Random, 95% CI       A         Total (95% CI)       19       253       100.0%       2.76 [0.31, 24.86]       IV       I													
Very Heavy PAE       Control       Odds Ratio       N, Random, 95% CI       Risk of Bias         Bandoli et al 2020       1       19       5       253       100.0%       2.76 [0.31, 24.86]       Image: Control Contred Unquantifiable	(A) Overall RoB												
Very Heavy PAE       Control       Odds Ratio       N, Random, 95% CI       Risk of Bias         Bandoli et al 2020       1       19       5       253       100.0%       2.76 [0.31, 24.86]       Image: Control Contred Unquantifiable		Vei	rv Hea	avv P <i>L</i>	F and	l Frequ	encv	of Strahism	us (%) (	1 study)			
Study or Subgroup         Events         Total         Events         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI         A           Bandoli et al 2020         1         19         5         253         100.0%         2.76 [0.31, 24.86]         IV, Random, 95% CI         A           Total (95% CI)         19         253         100.0%         2.76 [0.31, 24.86]         IV, Random, 95% CI         A           Total events         1         5         5         100.0%         2.76 [0.31, 24.86]         IV, Random, 95% CI         A           Risk of bias legend (A) Overall RoB         1         5         5         0         IV, Random, 95% CI         IV         IV <t< td=""><td></td><td></td><td>•</td><td>-</td><td></td><td>incqu</td><td>-</td><td></td><td>45 (70) (</td><td></td><td>atio</td><td>Risk of Bias</td></t<>			•	-		incqu	-		45 (70) (		atio	Risk of Bias	
Bandoli et al 2020       1       19       5       253       100.0%       2.76 [0.31, 24.86]         Total (95% Cl)       19       253       100.0%       2.76 [0.31, 24.86]         Total events       1       5       5       0.001       0.1       100         Test for overall effect: Z = 0.90 (P = 0.37)       V       V       V       V       V         Risk of bias legend (A) Overall RoB         Confirmed Unquantifiable       Control       Odds Ratio       Odds Ratio         Odds Ratio <td cols<="" td=""><td>Study or Subgroup</td><td></td><td></td><td></td><td></td><td>Weigh</td><td>t IV, I</td><td>Random, 95% Cl</td><td>1</td><td>IV, Random,</td><td>95% CI</td><td>A</td></td>	<td>Study or Subgroup</td> <td></td> <td></td> <td></td> <td></td> <td>Weigh</td> <td>t IV, I</td> <td>Random, 95% Cl</td> <td>1</td> <td>IV, Random,</td> <td>95% CI</td> <td>A</td>	Study or Subgroup					Weigh	t IV, I	Random, 95% Cl	1	IV, Random,	95% CI	A
Total events15Heterogeneity: Not applicable Test for overall effect: $Z = 0.90$ (P = 0.37)0.0010.11000 Control Very Heavy PAERisk of bias legend (A) Overall RoBConfirmed PAE Level Uncuantifiable ControlEventsConfirmed Unquantifiable EventsControlOdds Ratio Odds RatioRisk of Bias Odds RatioStudy or SubgroupEventsTotalVery TotalVery TotalVery TotalNote Reserve to the state of the state		1										•	
Total events15Heterogeneity: Not applicable Test for overall effect: $Z = 0.90$ (P = 0.37)0.0010.11000 Control Very Heavy PAERisk of bias legend (A) Overall RoBConfirmed PAE Level Uncuantifiable ControlEventsConfirmed Unquantifiable EventsControlOdds Ratio Odds RatioRisk of Bias Odds RatioStudy or SubgroupEventsTotalVery TotalVery TotalVery TotalNote Reserve to the state of the state	T / 1/05/ 00						_						
Heterogeneity: Not applicable Test for overall effect: Z = 0.90 (P = 0.37)         Risk of bias legend (A) Overall RoB         Confirmed PAE Level Uncurrentifiable       Very Heavy PAE         Confirmed Unquantifiable Control       Control       Odds Ratio Odds Ratio         Odds Ratio       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Very Heavy PAE         Study or Subgroup       Events       Total       Very Heavy PAE         Golden et al 1982       5       12       00       12       00       12       000%       N. Risk of Bias         Golden et al 1982       5       12       100.0%       18.33 [0.88, 380.70]       Odds Ratio       A         Total (95% CI)       12       100.0%       18.33 [0.88, 380.70]       Odds Ratio       Odd colspan="2">Odds Ratio         Total (95% CI)       12       10       0.001       0.01       0.01			19			100.0%	6 2	.76 [0.31, 24.86]					
Test for overall effect: Z = 0.90 (P = 0.37)         Confirmed PAE Level Unquantifiable         Confirmed PAE Level Unquantifiable         Confirmed Unquantifiable         Confirmed Unquantifiable         Confirmed Unquantifiable         Confirmed Unquantifiable         Control         Odds Ratio         Odds Ratio <td< td=""><td></td><td></td><td></td><td></td><td>5</td><td></td><td></td><td></td><td>L</td><td></td><td></td><td></td></td<>					5				L				
Confirmed PAE Level Urguantifiable       Control       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Events       Total       Control       Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Events       Total       Control       Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Golden et al 1982       5       12       12       12       12       10       III dol 1000       Control       Odds Ratio       N, Risk of Bias         Golden et al 1982       5       0       12       12       10       18.33 [0.88, 380.70]       0       0       0         Total (95% CI)       12       12       10       0       0       0       0       0       0       0       0       0 <th cols<="" td=""><td></td><td>•</td><td>: 0.37)</td><td></td><td></td><td></td><td></td><td></td><td>0.001</td><td></td><td></td><td></td></th>	<td></td> <td>•</td> <td>: 0.37)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.001</td> <td></td> <td></td> <td></td>		•	: 0.37)						0.001			
Confirmed PAE Level Unquantifiable       Control       Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Events       Total       Odds Ratio       Odds Ratio       Odds Ratio       Odds Ratio       Odds Ratio       Risk of Bias         Study or Subgroup       Events       Total       Veight       N, Random, 95% CI       A         Golden et al 1982       5       12       10       12       10       18.33 [0.88, 380.70]         Total (95% CI)       12       12       10       10         Total (95% CI)       12       10       10       0         Heterogeneity: Not applicable       0       0       0       0.001       0.1       10       0.001       0.01       0.01       0.01       0.01       0.01       0.01       0.01       0.01       <		2 - 0.00 () -	0.017							Control V	ery Heavy PA	E	
Confirmed Unquantifiable       Control       Control       Odds Ratio	Risk of bias legend												
Confirmed Unquantifiable Study or SubgroupEventsTotalControlOdds RatioOdds RatioRisk of BiasGolden et al 1982512012100.0%18.33 [0.88, 380.70]IV, Random, 95% CIAGolden et al 1982512012100.0%18.33 [0.88, 380.70]Image: Control Control Control Confirmed UnquantifiableTotal (95% CI)12012100.0%18.33 [0.88, 380.70]Image: Control Confirmed UnquantifiableTotal events5001100.0%18.33 [0.88, 380.70]Image: Control Confirmed UnquantifiableTotal events501100.0%18.33 [0.88, 380.70]Image: Control Confirmed UnquantifiableTotal events501100.0%1100.0%Total events501100.0%1Total events5011100.0%Test for overall effect: Z = 1.88 (P = 0.06)1111Risk of bias legend (A) Overall RoB1111(A) Overall RoB11111Total events111111Total events111111Total events111111Total events111111Total events111111Total events111	(A) Overall RoB												
Confirmed Unquantifiable Study or SubgroupEventsTotalControlOdds RatioOdds RatioRisk of BiasGolden et al 1982512012100.0%18.33 [0.88, 380.70]IV, Random, 95% CIAGolden et al 1982512012100.0%18.33 [0.88, 380.70]Image: Control Control Control Confirmed UnquantifiableTotal (95% CI)12012100.0%18.33 [0.88, 380.70]Image: Control Confirmed UnquantifiableTotal events5001100.0%18.33 [0.88, 380.70]Image: Control Confirmed UnquantifiableTotal events501100.0%18.33 [0.88, 380.70]Image: Control Confirmed UnquantifiableTotal events501100.0%1100.0%Total events501100.0%1Total events5011100.0%Test for overall effect: Z = 1.88 (P = 0.06)1111Risk of bias legend (A) Overall RoB1111(A) Overall RoB11111Total events111111Total events111111Total events111111Total events111111Total events111111Total events111	Com			ما ا ام		:fiabla	ام مر م		f Ctuch:	<i>(</i> 0/)	(1 at al)		
Study or Subgroup         Events         Total         Events         Total         Weight         IV, Random, 95% CI         A           Golden et al 1982         5         12         0         12         100.0%         18.33 [0.88, 380.70]         Image: Comparison of the state of t					-		and		r Strabi	• •	• • • •	Dick of Dice	
Golden et al 1982       5       12       0       12       100.0%       18.33 [0.88, 380.70]         Total (95% Cl)       12       12       100.0%       18.33 [0.88, 380.70]         Total events       5       0         Heterogeneity: Not applicable       0       0.001       0.1       1       10       1000         Test for overall effect: Z = 1.88 (P = 0.06)       Risk of bias legend       Querall RoB       Queral Rob			iquanui				/eiaht		CI				
Total (95% Cl)         12         12 100.0% 18.33 [0.88, 380.70]           Total events         5         0           Heterogeneity: Not applicable         0           Test for overall effect: Z = 1.88 (P = 0.06)         0.001           Risk of bias legend           (A) Overall RoB							-					- •	
Total events     5     0       Heterogeneity: Not applicable     0.001     0.1     1     10     1000       Test for overall effect: Z = 1.88 (P = 0.06)     0.001     0.1     1     10     1000       Risk of bias legend     (A) Overall RoB     0     0     0     0     0     0													
Heterogeneity: Not applicable       Image: transmitted in the second secon		F		12		12 10	00.0%	18.33 [0.88, 380.7	70]	1			
Test for overall effect: Z = 1.88 (P = 0.06)     0.001     0.1     1     1000       Risk of bias legend     Control     Confirmed Unquantifiable       (A) Overall RoB					U				<b>—</b>				
Risk of bias legend (A) Overall RoB			.06)						0.001				
(A) Overall RoB										Control	Commed of	Iquantinable	
Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.	(A) Overall ROB												
	<i>Notes:</i> Bandoli et al 202	0 reports 5 ti	rajecto	ries, use	d traject	ory D for	mode	rate (90g/week) a	and traject	tory E (313g/	/week) for vei	ry heavy PAE.	
INTERPUPILLARY DISTANCE	INTERPUPILLARY DI	<b>STANCE</b>											
Interpupillary Distance (mm) (m/SD)				Inte	rnuni	llary D	istar	ice (mm) (m					
		Цер	DA					· · · · ·		11 ctudy	۱		
Heavy PAE and Interpupillary Distance (mm) (m/SD) (1 study) Heavy PAE Control Std. Mean Difference Std. Mean Difference Risk of Bias			-		-	upillar	-		• • •			Risk of Rise	
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI A	Study or Subgroup	-				otal We							
Autti-Rämö et al 1992 44.31 0.63 17 45.87 0.32 48 100.0% -3.66 [-4.51, -2.81]										-		•	

48 100.0%

-3.66 [-4.51, -2.81]

-2

Ó

Heavy PAE Control

-4

2

4

 Total (95% Cl)
 17

 Heterogeneity: Not applicable

 Test for overall effect: Z = 8.41 (P < 0.00001)</td>

#### HYPOPLASTIC MIDFACE

#### Hypoplastic Midface (%) Moderate PAE and Frequency of Hypoplastic Midface (%) (1 study) Moderate PAE Control Odds Ratio Odds Ratio Risk of Bias Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup А Bandoli et al 2020 253 100.0% 5.84 [0.80, 42.55] 2 45 2 Total (95% CI) 45 253 100.0% 5.84 [0.80, 42.55] Total events 2 2 Heterogeneity: Not applicable 0.01 0.1 10 100 Test for overall effect: Z = 1.74 (P = 0.08) Control Moderate PAE Risk of bias legend

(A) Overall RoB

#### Very Heavy PAE and Frequency of Hypoplastic Midface (%) (1 study)

	Very Heavy	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	1	19	2	253	100.0%	6.97 [0.60, 80.61]		•
Total (95% CI)		19		253	100.0%	6.97 [0.60, 80.61]		
Total events	1		2					
Heterogeneity: Not ap	plicable							7
Test for overall effect:	Z=1.56 (P=	: 0.12)					0.001 0.1 1 10 100 Control Very Heavy PAE	-
Risk of bias legend								

(A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

#### **PTOSIS**

#### Ptosis (%) Moderate PAE and Frequency of Ptosis (%) (1 study) Moderate PAE Control Odds Ratio Odds Ratio **Risk of Bias** Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup Events А 253 100.0% Bandoli et al 2020 1 45 2 2.85 [0.25, 32.13] Total (95% CI) 45 253 100.0% 2.85 [0.25, 32.13] Total events 2 1 Heterogeneity: Not applicable 0.01 0.1 10 100 Test for overall effect: Z = 0.85 (P = 0.40) Control Moderate PAE Risk of bias legend (A) Overall RoB

#### Very Heavy PAE and Frequency of Ptosis (%) (1 study)

	Very 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	Α
Bandoli et al 2020	0	19	2	253	100.0%	2.58 [0.12, 55.63]		•
Total (95% CI)		19		253	100.0%	2.58 [0.12, 55.63]		
Total events	0		2					
Heterogeneity: Not ap Test for overall effect:	-	= 0.55)						
		,					Control Very Heavy P	AE

Risk of bias legend

(A) Overall RoB

	Confirmed Unquant	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Golden et al 1982	1	12	0	12	100.0%	3.26 [0.12, 88.35]		•
Total (95% CI)		12		12	100.0%	3.26 [0.12, 88.35]		
Total events	1		0					
Heterogeneity: Not app	licable							000
Test for overall effect: Z	Z = 0.70 (P = 0.48)						0.001 0.1 1 10 1 Control Confirmed U	

(A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

## EPICANTHAL FOLDS

				E	picant	hal Folds (%)		
	Mode	erate	PAE ar	nd Fre	auenc	v of Epicanthal F	Folds (%) (1 study)	
	Moderate		Contr			Odds Ratio		isk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
Bandoli et al 2020	25	45	144	253	100.0%	0.95 [0.50, 1.79]		
Total (95% CI)		45		253	100.0%	0.95 [0.50, 1.79]		
Total events	25		144					
Heterogeneity: Not ap	oplicable						0.5 0.7 1 1.5 2	
Test for overall effect:	Z=0.17 (P	= 0.87)					Control Moderate PAE	
<u>Risk of bias legend</u> (A) Overall RoB								
	Verv H	leavv	PAEa	nd Fr	eauena	v of Epicanthal	Folds (%) (1 study)	
	Very Heav		Cont			Odds Ratio		lisk of Bias
Study or Subgroup	Events		Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	Α
Bandoli et al 2020	11	19	144	253	100.0%	1.04 [0.40, 2.68]		•
Total (95% CI)		19		253	100.0%	1.04 [0.40, 2.68]	. ◆	
Total events	11		144					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.08 (P =	= 0.93)					Control Very Heavy PAE	
Risk of bias legend								
(A) Overall RoB								
Confirn	ned PAE I	Level	Ungua	ntifia	ble and	d Frequency of E	picanthal Folds (%) (1 study)	
	Confirmed U		-	Contro		Odds Ratio		Risk of Bia
Study or Subgroup	Events	-	Total E	vents	Total W	eight IV, Random, 95%	6 CI IV, Random, 95% CI	Α
Golden et al 1982	1		12	1	12 10	0.0% 1.00 [0.06, 18.	.08]	•

Golden et al 1982	1	12	1	12	100.0%	1.00 [0.06, 18.08]	—— <b>—</b> — •
Total (95% CI)		12		12	100.0%	1.00 [0.06, 18.08]	
Total events Heterogeneity: Not appli Test for overall effect: Z :			1				0.001 0.1 1 10 1000 Control Confirmed Unquantifiable
Risk of bias legend							

(A) Overall RoB

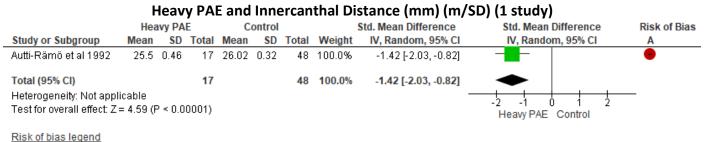
Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

## NASAL BRIDGE (0 STUDIES)

### **PROGNATHISM (0 STUDIES)**

#### **INNERCANTHAL DISTANCE**

#### Innercanthal distance (mm) (m/SD)



(A) Overall RoB

#### Short Innercanthal distance (%)

#### Moderate PAE and Frequency of Short Innercanthal Distance (%) (1 study) Moderate PAE Control Odds Ratio Odds Ratio Risk of Bias IV, Random, 95% CI Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Α Bandoli et al 2020 12 45 18 253 100.0% 4.75 [2.10, 10.74] Total (95% CI) 45 253 100.0% 4.75 [2.10, 10.74] Total events 12 18 Heterogeneity: Not applicable 0.01 10 100 0.1 Test for overall effect: Z = 3.74 (P = 0.0002) Control Moderate PAE

Risk of bias legend (A) Overall RoB

#### Very Heavy PAE and Frequency of Short Innercanthal Distance (%) (1 study)

	Very Heav	Control			Odds Ratio	Odds Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
Bandoli et al 2020	7	19	18	253	100.0%	7.62 [2.67, 21.72]		•
Total (95% CI)		19		253	100.0%	7.62 [2.67, 21.72]	•	
Total events	7		18					
Heterogeneity: Not ap	pplicable							ł
Test for overall effect	: Z = 3.80 (P :	= 0.0001	)				0.001 0.1 1 10 1000 Control Very Heavy PAE	
Dials of bing langed								

Risk of bias legend (A) Overall RoB

*Notes:* Bandoli et al 2020 had 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy. Aragon et al 1992a.

#### ANTEVERTED NARES

				Д	ntever	ted Nares (%)		
	Mod	erate	PAE an	d Fre	quency	of Anteverted N	Nares (%) (1 study)	
	Moderate	PAE	Contr	Control Odds Ratio Odds Ratio				Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	8	45	45	253	100.0%	1.00 [0.44, 2.29]		•
Total (95% CI)		45		253	100.0%	1.00 [0.44, 2.29]	+	
Total events Heterogeneity: Not a) Test for overall effect:	= 1.00)	45				0.01 0.1 1 10 Moderate PAE Control	100	

# Very Heavy PAE and Frequency of Anteverted Nares (%) (1 study)

	Very Heavy	y PAE	Contr	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	5	19	45	253	100.0%	1.65 [0.57, 4.82]	-	•
Total (95% CI)		19		253	100.0%	1.65 [0.57, 4.82]	◆	
Total events	5		45					
Heterogeneity: Not ap	plicable							<del></del>
Test for overall effect:	Z = 0.92 (P =	= 0.36)					0.001 0.1 1 10 10 Control Very Heavy PA	
Risk of bias legend								

(A) Overall RoB

# Confirmed PAE Level Unquantifiable and Frequency of Anteverted Nares (%) (1 study)

(	Confirmed Unquant	ifiable	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Golden et al 1982	8	12	0	12	100.0%	47.22 [2.24, 996.02]		- •
Total (95% CI)		12		12	100.0%	47.22 [2.24, 996.02]		
Total events	8		0					
Heterogeneity: Not appl	icable							
Test for overall effect: Z	= 2.48 (P = 0.01)						0.001 0.1 1 10 1 Favours Control Confirmed Unqua	000 antifiable
Risk of bias legend								

(A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

## **OUTERCANTHAL DISTANCE**

#### Outercanthal distance (mm) (m/SD) Heavy PAE and Outercanthal Distance (mm) (m/SD) (1 study) Heavy PAE Control Std. Mean Difference Std. Mean Difference Risk of Bias Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup Α Autti-Rämö et al 1992 67.56 0.95 17 69.48 0.42 48 100.0% -3.16 [-3.95, -2.37] Total (95% CI) 17 48 100.0% -3.16 [-3.95, -2.37] Heterogeneity: Not applicable -2 Ó ż 4 Test for overall effect: Z = 7.86 (P < 0.00001) Heavy PAE Control Risk of bias legend (A) Overall RoB MANDIBULAR ARC (0 STUDIES)

#### MAXILLARY ARC (0 STUDIES)

# **Diagnosed studies**

# **STRABISMUS**

					Stra	bismus (%)		
		FÆ	ASD an	d Fre	quency	of Strabismus (%	%) (1 study)	
	FAS	D	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2006	2	22	2	67	100.0%	3.25 [0.43, 24.57]		•
Total (95% CI)		22		67	100.0%	3.25 [0.43, 24.57]		
Total events Heterogeneity: Not ap Test for overall effect:	•	(P = 0.2	2 :5)				0.002 0.1 1 10 Control FASD	500

		FAS	and F	reque	ency of	Strabismus (%)	(5 studies)		
	FAS		Contr	ol		Odds Ratio	Od	ds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Rar	idom, 95% Cl	Α
Chambers et al 2019*	2	5	7	761	20.5%	71.81 [10.34, 498.61]			— <b>e</b>
May et al 2007	3	55	10	145	23.3%	0.78 [0.21, 2.94]	-		•
May et al 2013a	4	68	4	90	22.9%	1.34 [0.32, 5.58]		<b></b>	•
May et al 2020a*	1	4	4	278	17.9%	22.83 [1.93, 269.70]			- •
Viljoen et al 2005	2	64	0	146	15.3%	11.72 [0.55, 247.66]		+	— 😐
Total (95% CI)		196		1420	100.0%	6.19 [0.99, 38.58]			
Total events	12		25						
Heterogeneity: Tau <sup>2</sup> = 3.2	27; Chi <b>²</b> =	18.79,	df = 4 (P	= 0.000	09); I <sup>z</sup> = 7	9%	0.002 0.1		500
Test for overall effect: Z =	: 1.95 (P =	= 0.05)					Cont		500

(A) Overall RoB

# pFAS and Frequency of Strabismus (%) (5 studies)

	pFA	S	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	3	39	6	179	28.3%	2.40 [0.57, 10.06]			?
Chambers et al 2019*	3	44	7	761	29.1%	7.88 [1.97, 31.60]		<b></b> ■	•
May et al 2007	0	18	10	145	12.6%	0.35 [0.02, 6.20]			•
May et al 2013a	1	52	4	90	17.9%	0.42 [0.05, 3.88]			•
May et al 2020a*	0	22	4	278	12.1%	1.36 [0.07, 25.98]			•
Total (95% CI)		175		1453	100.0%	1.82 [0.56, 5.95]		•	
Total events	7		31						
Heterogeneity: Tau <sup>2</sup> = 0.76; Chi <sup>2</sup> = 7.04, df =	4 (P = 0.1	3); I <sup>2</sup> =	43%				+		
Test for overall effect: Z = 0.99 (P = 0.32)							0.002	0.1 1 10 Control pFAS	500

Risk of bias legend

(A) Overall RoB

# ARND/Others and Frequency of Strabismus (%) (3 studies)

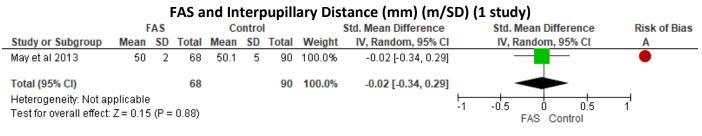
	ARND/Ot	hers	Cont	rol	-	Odds Ratio	Odds Ratio	<b>Risk of Bias</b>
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019* (ARND)	0	44	7	761	34.4%	1.13 [0.06, 20.11]	<b>+</b>	•
May et al 2013 (ARND)	0	22	4	278	32.7%	1.36 [0.07, 25.98]	<b>_</b>	•
May et al 2020a* (ARND)	0	35	4	90	32.8%	0.27 [0.01, 5.16]		•
Total (95% CI)		101		1129	100.0%	0.75 [0.14, 4.06]	-	
Total events	0		15					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	= 0.69, df=	= 2 (P =	0.71); I <sup>z</sup> =	:0%				-
Test for overall effect: Z = 0.33 (F	P = 0.74)						0.002 0.1 1 10 500 Control ARND/Others	
Risk of bias legend								

(A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005. May et al 2013a repots ARND and non-syndromal, used former.

## **INTERPUPILLARY DISTANCE**

# Interpupillary Distance (mm) (m/SD)



	pl	FAS			ontro		/ -		Aean Differen		(1 study) Std. Mean	Difference	Risk of Bia
Study or Subgroup			Total	Mean			Weigh		Random, 95		IV, Rando		A
Mayetal 2013	50	4	52	50.1	5		100.09		0.02 [-0.36, 0				•
T-4-1/054/ OB			50				400.00						
Total (95% CI)			52			90	100.09	% -	0.02 [-0.36, 0	.32]			1
Heterogeneity: Not appl		~								-1	-0.5 0	0.5	1
Test for overall effect: Z	= 0.12	(P =	0.90)								pFAS	Control	
<u>Risk of bias legend</u> ( <b>A</b> ) Overall RoB													
	AR	ND	/Oth	ers a	nd I	nter	oupilla	ary Di	stance (m	າm) (m	/SD) (1 stu	dy)	
	AR		thers		Con		-	Sto	. Mean Differ	ence	Std. Mean	Difference	Risk of Bi
Study or Subgroup	Mear			tal Me				-	V, Random, 9		IV, Rando	om, 95% Cl	A
May et al 2013 (ARND)	50	0	2	35 5	0.1	5 9	30 100	.0%	-0.02 [-0.41,	, 0.37]			•
Total (95% CI)				35			90 100	.0%	-0.02 [-0.41,	0.371			
Heterogeneity: Not appli	cable								0.02 [ 0.11,				
Test for overall effect: Z =		P = 0	).91)							-1	-0.5 ARND/Others	0 0.5 Control	1
											ARTICIDIOLITEIS	Control	
Risk of bias legend													
(A) Overall RoB													
			F	reau	ency	v Sho	rt Inte	er Pur	illary Dist	ance <	10%		
	EAS	and				, 					:10% (2 stu	dias)	
		FAS	iiie	•	itrol	1 3110		• •	Is Ratio		Odds Ra	•	Risk of Bia
Study or Subgroup	-		Total			tal M	leiaht		dom, 95% Cl		IV, Random,		A
May et al 2007		17	55	2			8.4%		7 [1.15, 4.90]		TV, Randolli,	55// 61	-
Mayetal 2007 Mayetal 2013a		41	68	1			37.2%		[4.92, 24.18]			- <b>-</b>	
Viljoen et al 2005		8	64				24.3%		[2.12, 49.93]	-			- ă
,		Ĩ							[2.1.2, 10.00]	,			•
Total (95% CI)			187		3	81 1	00.0%	5.98	[1.90, 18.80]	I			
Total events		66		3	-								
Heterogeneity: Tau <sup>2</sup> =					2 (P =	0.01);	$ ^{2} = 779$	6		0.01	0.1 1	10 '	100
Test for overall effect:	Z = 3.0	06 (F	° = 0.0	02)						0.01	Control F		
Risk of bias legend													
(A) Overall RoB													
	nFΔS	an	d Fre	allen	ncv c	of Sha	ort Int	ernu	nillary Dis	tance	<10% (2 stı	idies)	
	p1710	an		pFAS			itrol		Odds Ra			ds Ratio	Risk of Bia
Study or Subgroup				-			s Total	Weight		m, 95% Cl		dom, 95% Cl	Α
May et al 2010 - Italian Co	hort (FA	\S/pFi	AS)	9	39		0 179		111.82 [6.34	• •			
May et al 2007 May et al 2012a				0	18					0.01, 2.42]	•		
May et al 2013a				19	52	1	1 90	40.6%	· 4.13[1	1.77, 9.64]			•
Total (95% CI)					109		414	100.0%	4.01 [0.3	23, 70.57]			
Total events				28		3							
Heterogeneity: Tau² = 5.08 Test for everall offect: 7 = 1				2 (P = 0.	.005);	I <sup>z</sup> = 81%	, ,				0.01 0.1	1 10	100
Test for overall effect: Z = I	0.50 (F	- 0.3	7)								Cont	rol pFAS	
Risk of bias legend													
(A) Overall RoB													
	חואס		thore	اممد	Era			Shart	Intornun	illan, D	listance /1	ctudu)	
F		-	Other (Other		Cont	•	LY UI S		Interpup Odds Ratio	mary D	istance (1 Odds F		Risk of Bia
Study or Subgroup		vent					Weig		Random, 95%	CI	IV, Randon		A
May et al 2013a (ARNI		1		35	11		100.0		.60 [3.05, 18.9		ri, nanuon		<u> </u>
	- /	'	-			50	.00.0	~v (	.00 [0.00, 10.0	1			-
Total (95% CI)				35		90	100.0	% 7.	60 [3.05, 18.9	99]		$\bullet$	
Total events		1	0		11					-			

0.01

0.1

1 Controls ARND/Others

100

10

18 Total events Heterogeneity: Not applicable Test for overall effect: Z = 4.35 (P < 0.0001) 11

# Interpupillary Distance (centile)

# FASD and Interpupillary Distance (centile) (2 studies)

		FASD		C	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, Random, 95% CI	Α
Gomez et al 2020*	45.12	25.04	1389	63.13	23.79	602	98.7%	-0.73 [-0.83, -0.63]		•
May et al 2021*	41.7	19.2	6	60.5	24.9	71	1.3%	-0.76 [-1.60, 0.08]		•
Total (95% CI)			1395			673	100.0%	-0.73 [-0.83, -0.63]	•	
Heterogeneity: Tau² = Test for overall effect:				`	.95); l² =	= 0%			-4 -2 0 2 FASD Control	4

Risk of bias legend

(A) Overall RoB

# FAS and Interpupillary Distance (centile) (5 studies)

							1			
		FAS		0	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
Chambers et al 2019*	39.2	24.4	5	57.5	25.4	761	1.7%	-0.72 [-1.60, 0.16]		•
Gomez et al 2020*	38.18	23.87	579	63.13	23.79	602	90.4%	-1.05 [-1.17, -0.92]		•
May et al 2014	37.3	17.4	12	59.5	24.2	162	3.8%	-0.93 [-1.52, -0.33]		•
May et al 2020a*	21.5	18.5	4	58.5	24.6	278	1.4%	-1.50 [-2.50, -0.51]		•
May et al 2020b*	36.9	24.6	8	57.3	25.8	413	2.7%	-0.79 [-1.49, -0.09]		•
Total (95% CI)			608			2216	100.0%	-1.04 [-1.15, -0.92]	•	
Heterogeneity: Tau² = 0. Test for overall effect: Z =	•			P = 0.74	;	%			-2 -1 0 1 2 FAS Control	2

Risk of bias legend (A) Overall RoB

# pFAS and Interpupillary Distance (centile) (5 studies)

								•	
	pFAS		0	Control			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
48.5	30.2	44	57.5	25.4	761	19.2%	-0.35 [-0.65, -0.05]		•
50.75	24.68	479	63.13	23.79	602	51.4%	-0.51 [-0.63, -0.39]	•	•
37.3	15.1	23	59.5	24.2	162	10.3%	-0.95 [-1.40, -0.50]		•
48.7	25.5	22	58.5	24.6	278	10.8%	-0.40 [-0.83, 0.04]		•
47.7	24.3	16	57.3	25.8	413	8.4%	-0.37 [-0.87, 0.13]		•
		584			2216	100.0%	-0.50 [-0.66, -0.35]	•	
01; Chi <b>ž</b>	= 5.30,	df = 4 (	P = 0.26	i); <b>I</b> ² = 2	4%				<u> </u>
= 6.37 (P	< 0.000	001)						PFAS Control	2
	Mean 48.5 50.75 37.3 48.7 47.7 01; Chi <sup>z</sup>	48.5 30.2 50.75 24.68 37.3 15.1 48.7 25.5 47.7 24.3 01; Chi <sup>2</sup> = 5.30,	Mean         SD         Total           48.5         30.2         44           50.75         24.68         479           37.3         15.1         23           48.7         25.5         22           47.7         24.3         16           584	Mean         SD         Total         Mean           48.5         30.2         44         57.5           50.75         24.68         479         63.13           37.3         15.1         23         59.5           48.7         25.5         22         58.5           47.7         24.3         16         57.3           584           01; Chi <sup>a</sup> = 5.30, df = 4 (P = 0.26)	Mean         SD         Total         Mean         SD           48.5         30.2         44         57.5         25.4           50.75         24.68         479         63.13         23.79           37.3         15.1         23         59.5         24.2           48.7         25.5         22         58.5         24.6           47.7         24.3         16         57.3         25.8           584           01; Chi <sup>2</sup> = 5.30, df = 4 (P = 0.26); I <sup>2</sup> = 2	Mean         SD         Total         Mean         SD         Total           48.5         30.2         44         57.5         25.4         761           50.75         24.68         479         63.13         23.79         602           37.3         15.1         23         59.5         24.2         162           48.7         25.5         22         58.5         24.6         278           47.7         24.3         16         57.3         25.8         413           584         2216           01; Chi <sup>2</sup> = 5.30, df = 4 (P = 0.26); I <sup>2</sup> = 24%	Mean         SD         Total         Mean         SD         Total         Weight           48.5         30.2         44         57.5         25.4         761         19.2%           50.75         24.68         479         63.13         23.79         602         51.4%           37.3         15.1         23         59.5         24.2         162         10.3%           48.7         25.5         22         58.5         24.6         278         10.8%           47.7         24.3         16         57.3         25.8         413         8.4%           584         2216         100.0%           01; Chi <sup>2</sup> = 5.30, df = 4 (P = 0.26); I <sup>2</sup> = 24%         24%         10         10	Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI           48.5         30.2         44         57.5         25.4         761         19.2% $-0.35$ [-0.65, -0.05]           50.75         24.68         479         63.13         23.79         602         51.4% $-0.51$ [-0.63, -0.39]           37.3         15.1         23         59.5         24.2         162         10.3% $-0.95$ [-1.40, -0.50]           48.7         25.5         22         58.5         24.6         278         10.8% $-0.40$ [-0.83, 0.04]           47.7         24.3         16         57.3         25.8         413         8.4% $-0.37$ [-0.87, 0.13]           584         2216         100.0%         -0.50 [-0.66, -0.35]           01; Chi <sup>2</sup> = 5.30, df = 4 (P = 0.26); I <sup>2</sup> = 24%         54%         -0.50 [-0.66, -0.35]	Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI           48.5         30.2         44         57.5         25.4         761         19.2%         -0.35 [-0.65, -0.05]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.39]         -0.35 [-0.63, -0.37]         -0.35 [-0.63, -0.35]         -0.35 [-0.63, -0.35]         -0.35 [-0.66, -0.35]

Risk of bias legend (A) Overall RoB

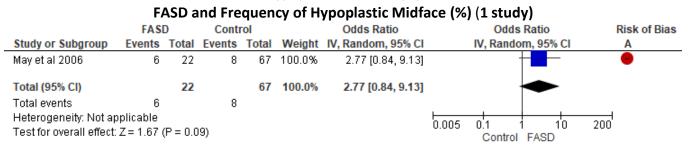
# ARND/Others and Interpupillary Distance (centile) (5 studies)

	ARN	ID/Othe	rs	0	Control			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019* (ARND)	59.8	26.6	44	57.5	25.4	761	22.7%	0.09 [-0.21, 0.39]	- <b>-</b>	•
Gomez et al 2020* (ARND)	49.13	24.69	331	63.13	23.79	602	26.8%	-0.58 [-0.72, -0.44]	-	•
May et al 2014 (ARND)	53.7	25	13	59.5	24.2	162	15.4%	-0.24 [-0.80, 0.33]		•
May et al 2020a* (ARND)	56.7	24.5	12	58.5	24.6	278	15.1%	-0.07 [-0.65, 0.50]		•
May et al 2020b* (ARND)	50.3	25.8	25	57.3	25.8	413	19.8%	-0.27 [-0.67, 0.13]	-•+	•
Total (95% CI)			425			2216	100.0%	-0.24 [-0.57, 0.09]	•	
Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup>	= 18.39,	df = 4 (l	P = 0.01	01); I <sup>z</sup> =	78%					<u>+</u>
Test for overall effect: Z = 1.40 (P	= 0.16)								ARND/Others Control	2

Risk of bias legend (A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005.

# Hypoplastic Midface (%)



# Risk of bias legend

(A) Overall RoB

# FAS and Frequency of Hypoplastic Midface (%) (7 studies)

	FAS	5	Cont	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
May et al 2007	25	55	28	145	18.9%	3.48 [1.78, 6.82]	] –•– 😑
May et al 2013a	56	68	38	90	17.9%	6.39 [3.01, 13.53]	] – – – –
May et al 2014	7	12	43	162	12.4%	3.87 [1.17, 12.86]	] 🗕 🗕
May et al 2015	4	7	22	90	9.1%	4.12 [0.86, 19.85]	] +
May et al 2017	99	129	22	104	19.6%	12.30 [6.60, 22.94]	] – – 😑
May et al 2020c*	6	11	130	521	12.3%	3.61 [1.08, 12.02]	] – – –
Viljoen et al 2005	23	64	2	164	9.8%	45.44 [10.29, 200.61]	]
Total (95% CI)		346		1276	100.0%	6.60 [3.64, 11.96]	」 ◆
Total events	220		285				
Heterogeneity: Tau <sup>2</sup> =	= 0.37; Ch	i² = 15.8	87, df = 6	(P = 0.	01); I <sup>z</sup> = 6	2%	
Test for overall effect				-			0.005 0.1 1 10 200 Control FAS

# Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Hypoplastic Midface (%) (5 studies)

	pFA	S	Contr	ol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
May et al 2007	9	18	28	145	13.3%	4.18 [1.52, 11.49]			•
May et al 2013a	37	52	38	90	23.9%	3.38 [1.62, 7.01]			•
May et al 2015	7	19	22	90	12.4%	1.80 [0.63, 5.15]		+	•
May et al 2017	61	100	22	104	31.8%	5.83 [3.14, 10.82]			•
May et al 2020c*	11	23	130	521	18.6%	2.76 [1.19, 6.40]			•
Total (95% CI)		212		950	100.0%	3.68 [2.51, 5.39]		•	
Total events	125		240						
Heterogeneity: Tau² =	0.02; Ch	i <sup>2</sup> = 4.41	6, df = 4 (	P = 0.3	5); I² = 10	%	0.005		200
Test for overall effect:	Z = 6.68	(P < 0.0	10001)				0.000	Control pFAS	200

# Risk of bias legend

(A) Overall RoB

# ARND/Others and Frequency of Hypoplastic Midface (%) (3 studies)

						.,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
	ARND/Ot	hers	Contr	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013a (ARND)	22	35	38	90	37.3%	2.32 [1.04, 5.17]		•
May et al 2020c* (ARND)	5	10	130	521	15.3%	3.01 [0.86, 10.55]	_ <b>_</b>	•
May et al 2017 (ARND)	23	55	22	104	47.4%	2.68 [1.31, 5.47]		•
Total (95% CI)		100		715	100.0%	2.58 [1.58, 4.22]	•	
Total events	50		190					
Heterogeneity: Tau <sup>2</sup> = 0.00	; Chi <b>²</b> = 0.1	4, df = 3	2 (P = 0.9	3); I <b>2</b> =	0%			<del></del>
Test for overall effect: Z = 3	.79 (P = 0.)	0002)					0.005 0.1 1 10 2 Control ARND/Others	200
							Control ARND/Others	

Risk of bias legend (A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005. May et al 2013a repots ARND and non-syndromal, used former.

#### Ptosis (%) FASD and Frequency of Ptosis (%) (1 study) FASD 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 May et al 2006 3 22 0 67 100.0% 24.23 [1.20, 489.48] Total (95% CI) 22 67 100.0% 24.23 [1.20, 489.48] Total events 0 3 Heterogeneity: Not applicable 0.002 10 0.1 i. 500 Test for overall effect: Z = 2.08 (P = 0.04) Control FASD Risk of bias legend

(A) Overall RoB

# FAS and Frequency of Ptosis (%) (6 studies)

		•			19661167		Junaic	<b>9</b> /	
	FAS	5	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Chambers et al 2019*	2	5	18	761	10.6%	27.52 [4.33, 174.89]			- 😑
May et al 2007	10	55	3	145	19.6%	10.52 [2.77, 39.89]		<b>_--</b>	•
May et al 2013a	10	68	5	90	26.7%	2.93 [0.95, 9.02]			•
May et al 2017	23	129	3	104	22.6%	7.31 [2.13, 25.08]		<b> </b> − <b>∎</b> −	•
May et al 2020b*	3	8	33	413	16.2%	6.91 [1.58, 30.20]			•
Viljoen et al 2005	4	64	0	146	4.3%	21.79 [1.16, 411.03]			- •
Total (95% CI)		329		1659	100.0%	7.34 [3.98, 13.57]		•	
Total events	52		62						
Heterogeneity: Tau <sup>2</sup> = 0.	04; Chi <sup>2</sup> =	5.33, 0	#f = 5 (P =	: 0.38);	I²=6%		+		
Test for overall effect: Z	= 6.37 (P <	< 0.000	101)				0.002	0.1 1 10 Control FAS	500

Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Ptosis (%) (6 studies)

	pFA	S	Cont	rol		Odds Ratio	-	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	3	39	6	179	15.3%	2.40 [0.57, 10.06]			?
Chambers et al 2019*	4	44	18	761	24.7%	4.13 [1.33, 12.77]			•
May et al 2007	1	18	3	145	5.9%	2.78 [0.27, 28.29]			•
May et al 2013a	4	52	5	90	17.0%	1.42 [0.36, 5.53]			•
May et al 2017	5	100	3	104	14.8%	1.77 [0.41, 7.62]		<b></b>	•
May et al 2020b*	4	16	33	413	22.4%	3.84 [1.17, 12.57]			•
Total (95% CI)		269		1692	100.0%	2.69 [1.53, 4.71]		•	
Total events	21		68						
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.09, df =	5 (P = 0.8	84); I <sup>2</sup> =	0%				0.002		500
Test for overall effect: Z = 3.46 (P = 0.0005)							0.002	Control pFAS	500

Risk of bias legend (A) Overall RoB

# ARND/Others and Frequency of Ptosis (%) (4 studies)

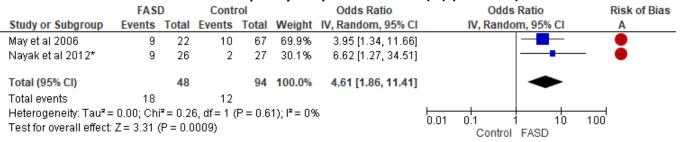
		/					(1000000)	
	ARND/Ot	hers	Cont	rol		Odds Ratio	Odds Ratio Risk of Bia	1S
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A	
Chambers et al 2019* (ARND)	0	44	18	761	10.6%	0.45 [0.03, 7.62]		
May et al 2013 (ARND)	0	35	5	90	10.0%	0.22 [0.01, 4.07]		
May et al 2017 (ARND)	2	55	3	104	25.7%	1.27 [0.21, 7.84]	_ <b>_</b> •	
May et al 2020b* (ARND)	3	25	33	413	53.7%	1.57 [0.45, 5.52]	_∎_ ●	
Total (95% CI)		159		1368	100.0%	1.07 [0.43, 2.69]	. ◆	
Total events	5		59					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> Test for overall effect: Z = 0.14 (P		: 3 (P =	0.60); I² =	:0%			0.002 0.1 1 10 500 Control ARND/Others	

Risk of bias legend (A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005. May et al 2013a repots ARND and non-syndromal, used former.

# Epicanthal Folds (%)





#### Risk of bias legend

(A) Overall RoB

# FAS and Frequency of Epicanthal Folds (%) (4 studies)

	FAS		Cont	lor		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	34	55	71	145	30.1%	1.69 [0.90, 3.18]	<b>↓</b> ■	•
May et al 2013a	43	68	35	90	28.6%	2.70 [1.41, 5.18]		•
May et al 2014	5	12	28	162	8.2%	3.42 [1.01, 11.55]		•
Viljoen et al 2005	34	64	45	146	33.2%	2.54 [1.39, 4.65]		•
Total (95% CI)		199		543	100.0%	2.34 [1.66, 3.32]	•	
Total events	116		179					
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>z</sup>	<sup>i</sup> = 1.66	i, df = 3 (	P = 0.6	5); I <sup>2</sup> = 09	6		
Test for overall effect	Z = 4.80 (F	P < 0.0I	0001)				0.01 0.1 1 10 1 Control FAS	100

#### Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Epicanthal Folds (%) (3 studies)

	pFA	s	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	10	18	71	145	25.2%	1.30 [0.49, 3.49]		•
May et al 2013a	33	52	35	90	49.1%	2.73 [1.35, 5.53]	<b> </b> − <b>∎</b> −	•
May et al 2014	7	23	28	162	25.6%	2.09 [0.79, 5.56]	+	•
Total (95% CI)		93		397	100.0%	2.12 [1.29, 3.47]	•	
Total events	50		134					
Heterogeneity: Tau² =	0.00; Chi	r = 1.43	3, df = 2 (	(P = 0.4	9); <b>i</b> ² = 09	6		100
Test for overall effect:	Z = 2.97 (	(P = 0.0	103)				Control pFAS	100

Risk of bias legend

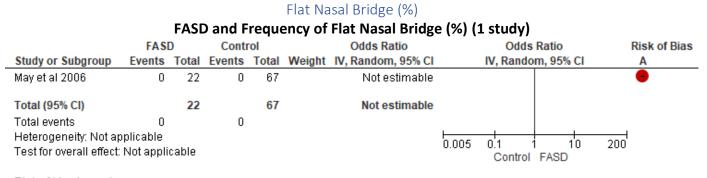
(A) Overall RoB

### ARND/Others and Frequency of Epicanthal Folds (%) (2 studies)

Odds Ratio	Risk of Bias
	nak of blua
V, Random, 95% Cl	Α
	•
	•
Control ARND/Others	

Risk of bias legend (A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005. May et al 2013a repots ARND and non-syndromal, used former.



#### Risk of bias legend (A) Overall RoB

# FAS and Frequency of Flat Nasal Bridge (%) (4 studies)

							(, , (, , , , , , , , , , , , , , , , ,	
	FAS	5	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events Total		Events Total		Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	27	55	39	145	33.4%	2.62 [1.38, 4.99]		•
May et al 2013a	41	68	33	90	33.3%	2.62 [1.37, 5.01]		•
May et al 2015	1	7	2	190	4.6%	15.67 [1.24, 197.53]		- •
Viljoen et al 2005	25	64	13	146	28.7%	6.56 [3.07, 14.01]		•
Total (95% CI)		194		571	100.0%	3.70 [2.10, 6.55]	•	
Total events	94		87					
Heterogeneity: Tau <sup>2</sup> :	= 0.14; Ch	i <sup>2</sup> = 5.5 <sup>1</sup>	1, df = 3 (	(P = 0.1	4); l <sup>2</sup> = 46	i%		
Test for overall effect	•			•			0.005 0.1 1 10 Control FAS	200

# Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Flat Nasal Bridge (%) (4 studies)

	pFA	S	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	0	39	7	179	11.0%	0.29 [0.02, 5.20]		?
May et al 2007	12	18	39	145	31.7%	5.44 [1.91, 15.48]	<b></b> ■	•
May et al 2013a	29	52	33	90	37.8%	2.18 [1.09, 4.36]	- <b>-</b> -	•
May et al 2015	3	19	2	190	19.6%	17.63 [2.74, 113.28]		•
Total (95% CI)		128		604	100.0%	3.51 [1.17, 10.55]	•	
Total events	44		81					
Heterogeneity: Tau² = 0.71; Chi² = 8.03, df = Test for overall effect: Z = 2.24 (P = 0.02)	3 (P = 0.0	15); I² =	63%				0.005 0.1 1 10 20 Control pFAS	00

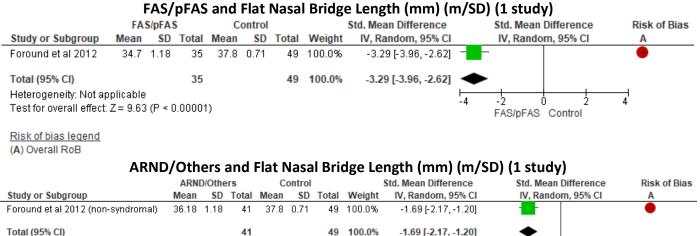
#### Risk of bias legend (A) Overall RoB

# ARND/Others and Frequency of Flat Nasal Bridge (%) (1 study)

		/						
	ARND/Ot	hers	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events Tota		Events	vents Total		IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013 (ARND)	20	35	33	90	100.0%	2.30 [1.04, 5.10]		•
Total (95% CI)		35		90	100.0%	2.30 [1.04, 5.10]	•	
Total events	20		33					
Heterogeneity: Not appli Test for overall effect: Z =		0.04)					0.005 0.1 1 10 2 Control ARND/Others	200

### Risk of bias legend

(A) Overall RoB Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005. May et al 2013a repots ARND and non-syndromal, used former.



Heterogeneity: Not applicable Test for overall effect: Z = 6.81 (P < 0.00001)

Risk of bias legend (A) Overall RoB

Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005. Foround et al 2012 reported measures at 5yrs and 9yrs, used 5yrs in meta-analysis.

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pFAS Control

ARND/Others Control

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# Nasal Bridge Length (z-score)

							50	5		
			FA	S and	Nasal	Bridg	ge Leng	gth (z-score) (1 s	tudy)	
		FAS			Control	-		Std. Mean Difference	Std. Mean Difference	Risk of Bia
Study or Subgroup	Mear	n SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	Α
Moore et al 2002*	-1.1162	2 1.605	i 39	-0.0843	0.9709	31	100.0%	-0.75 [-1.24, -0.26]		•
Total (95% CI)			39			31	100.0%	-0.75 [-1.24, -0.26]	-	
Heterogeneity: Not ap	pplicable									<u> </u>
Test for overall effect		(P = 0.0)	03)						-2 -1 0 1	2
									FAS Control	
Risk of bias legend										
(A) Overall RoB										
AIOVEIaIIIXOD			nE	hac 2	Nacal	Brid	a lon	gth (z-score) (1	study)	
			- Pi /		ivasai	Dilu	ge Len	gtii (2-30012) (1	studyj	
		pFAS		C	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Moore et al 2002*	-0.3	1.3458	59	-0.0843	0.9709	31	100.0%	-0.17 [-0.61, 0.26]		•
Total (95% CI)			59			31	100.0%	-0.17 [-0.61, 0.26]	-	
Heterogeneity: Not a	pplicable									<u> </u>
Toot for overall effect		(D - 0.4)	2						-2 -1 0 1	2

Test for overall effect: Z = 0.78 (P = 0.43)

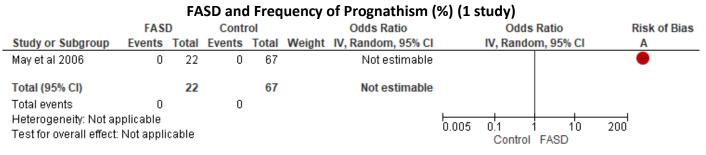
Risk of bias legend

(A) Overall RoB

Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005

# PROGNATHISM

# Prognathism (%)



FAS and Frequency of Prognathism (%) (3 studies)														
	FAS Control Odds Ratio Odds Ratio													
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A							
May et al 2007	6	55	3	145	52.0%	5.80 [1.40, 24.06]								
May et al 2013a	5	68	2	90	37.7%	3.49 [0.66, 18.58]	+ •							
Viljoen et al 2005	1	64	0	146	10.2%	6.92 [0.28, 172.21]	•							
Total (95% CI)		187		381	100.0%	4.87 [1.75, 13.61]	◆							
Total events	12		5											
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i² = 0.2	6, df = 2 (	(P = 0.8	8); I <sup>z</sup> = 09	6								
Test for overall effect:	Z = 3.02	(P = 0.0	)03)				Control FAS							

(A) Overall RoB

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# pFAS and Frequency of Prognathism (%) (1 study)

		· · · ·						
	pFA	s	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	0	18	3	145	26.9%	1.10 [0.05, 22.16]		•
May et al 2013a	3	52	2	90	73.1%	2.69 [0.44, 16.68]		•
Total (95% CI)		70		235	100.0%	2.12 [0.45, 10.06]	-	
Total events	3		5					
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi	i <sup>z</sup> = 0.2	5, df = 1 (	P = 0.6	2); I <sup>2</sup> = 09	6		200
Test for overall effect:	Z = 0.94 (	(P = 0.3	35)				Control pFAS	200

#### Risk of bias legend (A) Overall RoB

# ARND/Others and Frequency of Prognathism (%) (1 study)

	ARND/Oth	hers	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013 (ARND)	1	35	2	90	100.0%	1.29 [0.11, 14.74]		•
Total (95% CI)		35		90	100.0%	1.29 [0.11, 14.74]		
Total events	1		2					
Heterogeneity: Not applie	cable							200
Test for overall effect: Z =	= 0.21 (P = 0	0.84)					Control ARND/Others	.00

# Risk of bias legend

(A) Overall RoB

*Notes:* Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005. May et al 2013a repots ARND and non-syndromal, used former.

# **INNERCANTHAL DISTANCE**

# Innercanthal distance (mm) (m/SD)

	F	ASD		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Nayak et al 2012*	25.9	2.07	26	25.25	1.93	27	63.0%	0.65 [-0.43, 1.73]	-+	•
Popova et al 2019	28.4	3.1	21	28.3	2.2	83	37.0%	0.10 [-1.31, 1.51]		•
Total (95% CI)			47			110	100.0%	0.45 [-0.41, 1.30]	-	
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cl	hi² = O	.37, df=	= 1 (P =	0.54);	l <sup>z</sup> = 0%			<del>, , , , ,</del>	- <u>+</u>

#### Risk of bias legend (A) Overall RoB

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# FAS and Innercanthal Distance (mm) (m/SD) (2 studies)

	F/	AS	Control					Mean Difference	Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD T	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α	
Blanck-Lubarsch 2019*	28.8	2.3	28	31	2.3	30	48.8%	-2.20 [-3.38, -1.02]		•	
May et al 2013	28	2	68	29.1	5	90	51.2%	-1.10 [-2.24, 0.04]		•	
Total (95% CI)			96			120	100.0%	-1.64 [-2.71, -0.56]	<b>•</b>		
Heterogeneity: Tau <sup>2</sup> = 0.25	5; Chi <b>²</b> = 1	I.72, d	df = 1 (	(P = 0.1	9); <b>I</b> ²∶	= 42%					
Test for overall effect: Z = 2	2.98 (P =	0.003)	i)						FAS Control	7	

	pl	AS a	nd Inr	nerca	Intha	l Dista	nce (mm) (m/SI	D) (2 studies)	
	pFAS		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Foround et al 2012	30.74 0.71	35	31.22	0.35	49	97.2%	-0.48 [-0.73, -0.23]	—	•
May et al 2013	28.8 4	52	29.1	5	90	2.8%	-0.30 [-1.80, 1.20]	•	$\rightarrow igodol $
Total (95% CI)		87			139	100.0%	-0.47 [-0.73, -0.22]	<b>•</b>	
Heterogeneity: Tau² = Test for overall effect:		•		0.82);	I <sup>2</sup> = 0%	I		-1 -0.5 0 0.5 pFAS Control	<b>+</b> 1

(A) Overall RoB

# ARND/Others and Innercanthal Distance (mm) (m/SD) (2 studies)

	ARN	D/Othe	ers	С	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Foround et al 2012 (non-syndromal)	31.46	0.59	41	31.22	0.35	49	54.6%	0.24 [0.03, 0.45]		•
May et al 2013 (ARND)	27.3	2	35	29.1	5	90	45.4%	-1.80 [-3.03, -0.57]		•
Total (95% CI)			76			139	100.0%	-0.69 [-2.68, 1.30]		
Heterogeneity: Tau <sup>2</sup> = 1.88; Chi <sup>2</sup> = 10.3 Test for overall effect: $Z = 0.68$ (P = 0.5	•	(P = 0	).001);1	I² = 90%					-4 -2 0 2	4
Testion overall ellect. $\Sigma = 0.00$ (i = 0.3	0)								ARND/Others Control	

Risk of bias legend

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005. May et al 2013a reports ARND and non-syndromal, used former. Blanck-Lubarsch et al 2019a. Foround et al 2012 reported measures at 5yrs and 9yrs, used 5yrs in meta-analysis.

# Short innercanthal distance (%)

#### FASD and Frequency of Short Innercanthal Distance <10% (2 studies) FASD Control Odds Ratio Odds Ratio Risk of Bias Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup А Popova et al 2019 1.08 [0.41, 2.81] 10 21 38 83 66.0% May et al 2006 4 22 5 67 34.0% 2.76 [0.67, 11.35] Total (95% CI) 150 100.0% 43 1.48 [0.62, 3.55] Total events 14 43 Heterogeneity: Tau<sup>2</sup> = 0.06; Chi<sup>2</sup> = 1.16, df = 1 (P = 0.28); l<sup>2</sup> = 14% 0.05 20 0.2 5 Test for overall effect: Z = 0.88 (P = 0.38) Control FASD

#### Risk of bias legend (A) Overall RoB

# FAS and Frequency of Short Innercanthal Distance <10% (3 studies)

	I AS al	IU I I C	quent	y 01 3		leicantinai Distai	ice <10/0 (3 studies)	
	FAS		Contr	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	17	55	23	145	45.7%	2.37 [1.15, 4.90]	<b></b>	•
May et al 2013a	22	68	18	90	45.7%	1.91 [0.93, 3.95]	<b>⊢</b> ∎−−	•
Viljoen et al 2005	5	64	2	146	8.6%	6.10 [1.15, 32.33]		— •
Total (95% CI)		187		381	100.0%	2.33 [1.43, 3.81]	•	
Total events	44		43					
Heterogeneity: Tau <sup>2</sup> :	= 0.00; Chi	<sup>2</sup> = 1.5	7, df = 2 (	(P = 0.4)	6); I <sup>2</sup> = 09	6		+
Test for overall effect	: Z = 3.39 (	(P = 0.0	1007)				Control FAS	20

#### Risk of bias legend (A) Overall RoB

# pFAS and Frequency of Short Innercanthal Distance <10% (3 study)

	pFAS		Control		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	0	18	23	145	8.9%	0.14 [0.01, 2.42]	<b>←</b>	•
May et al 2010 - Italian Cohort (FAS/pFAS)	8	39	20	179	44.1%	2.05 [0.83, 5.08]	+	?
May et al 2013a	11	52	18	90	46.9%	1.07 [0.46, 2.49]		•
Total (95% CI)		109		414	100.0%	1.19 [0.48, 2.94]	-	
Total events	19		61					
Heterogeneity: Tau <sup>2</sup> = 0.27; Chi <sup>2</sup> = 3.52, df = Test for overall effect: Z = 0.38 (P = 0.70)	2 (P = 0.1	7);   <b>2</b> =	43%				0.05 0.2 1 5 Control pFAS	20

AR	RND/Oth	ners a	nd Fre	quen	cy of Sl	hort Innercantha	al Distance (1 study)	
	ARND/Ot	hers	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013a (ARND)	9	38	18	90	100.0%	1.24 [0.50, 3.08]		•
Total (95% CI)		38		90	100.0%	1.24 [0.50, 3.08]	-	
Total events Heterogeneity: Not applica Test for overall effect: Z = I		.64)	18				0.05 0.2 1 5 Control ARND/Others	20

(A) Overall RoB

Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005.

Innercanthal Distance (centile)

# FAS and Innercanthal Distance (Centile) (2 studies)

									. otaaicoj		
		FAS		0	Control		:	Std. Mean Difference	Std. Mea	n Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Ran	lom, 95% Cl	Α
Gomez et al 2020*	48.39	22.87	580	59.8	21.46	604	61.1%	-0.51 [-0.63, -0.40]			•
May et al 2014	30.1	20.4	12	55.5	22.1	162	38.9%	-1.15 [-1.75, -0.55]			•
Total (95% CI)			592			766	100.0%	-0.76 [-1.37, -0.15]			
Heterogeneity: Tau <sup>2</sup> =	= 0.15; C	hi² = 4.1	6, df=	1 (P = 0	.04); l² =	= 76%					
Test for overall effect:	Z= 2.48	6 (P = 0.	01)						FA	S Control	2

Risk of bias legend

(A) Overall RoB

# pFAS and Innercanthal Distance (Centile) (2 studies)

	pFAS Control							Std. Mean Difference	Std. Mean Difference	<b>Risk of Bias</b>
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Gomez et al 2020*	56.08	22.16	479	59.8	21.46	604	72.7%	-0.17 [-0.29, -0.05]		•
May et al 2014	44.7	20.4	23	55.5	22.1	162	27.3%	-0.49 [-0.93, -0.05]		•
Total (95% CI)			502			766	100.0%	-0.26 [-0.54, 0.02]	•	
Heterogeneity: Tau <sup>2</sup> =	= 0.02; C	hi <b>²</b> = 1.9	0, df=	1 (P = 0	.17); <b>I</b> ≊ ⊧	= 47%		H		
Test for overall effect	: Z = 1.81	(P = 0.	07)					-	pFAS Control	2

Risk of bias legend (A) Overall RoB

# ARND/Others and Innercanthal Distance (Centile) (2 studies)

	ARN	D/Othe	rs	0	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Gomez et al 2020* (ARND)	48.84	22.77	332	59.8	21.46	604	94.6%	-0.50 [-0.64, -0.36]		•
May et al 2014 (ARND)	41.5	19.1	13	55.5	22.1	162	5.4%	-0.64 [-1.21, -0.07]		•
Total (95% CI)			345			766	100.0%	-0.51 [-0.64, -0.37]	◆	
Heterogeneity: Tau <sup>2</sup> = 0.00; C Test for overall effect: Z = 7.5		•		l.65); l² =	= 0%				-2 -1 0 1 ARND/Others Control	2

Risk of bias legend (A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005.

#### Innercanthal distance (z-score) FAS and Innercanthal Distance (z-score) (1 study) FAS Control Mean Difference Mean Difference **Risk of Bias** Study or Subgroup SD Total Weight IV, Random, 95% CI IV, Random, 95% CI Mean SD Total Mean A Moore et al 2002\* 31 100.0% -0.17 [-0.76, 0.41] -1.1865 1.1638 41 -1.0121 1.3259 Total (95% CI) -0.17 [-0.76, 0.41] 41 31 100.0% Heterogeneity: Not applicable -4 -2 ż 4 Ó Test for overall effect: Z = 0.58 (P = 0.56) FAS Control

		pFAS		C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
Moore et al 2002*	-0.8877	1.3446	59	-1.0121	1.3259	31	100.0%	0.12 [-0.45, 0.70]		•
Total (95% CI)			59			31	100.0%	0.12 [-0.45, 0.70]	+	
Heterogeneity: Not a	pplicable									
Test for overall effect	: Z = 0.42 (I	P = 0.67)							pFAS Control	4

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Risk of bias legend (A) Overall RoB

Notes: Moore et al 2002 used z-score Farkas 1981 norms.

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### **ANTEVERTED NARES**

#### Anteverted Nares (%) FASD and Frequency of Anteverted Nares (%) (1 study) FASD Control Odds Ratio Odds Ratio Risk of Bias Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup Α May et al 2006 5.81 [1.74, 19.43] 8 22 6 67 100.0% Total (95% CI) 22 67 100.0% 5.81 [1.74, 19.43] Total events 8 6 Heterogeneity: Not applicable 0.001 1000 0.1 10 Test for overall effect: Z = 2.86 (P = 0.004) Control FASD

Risk of bias legend (A) Overall RoB

### FAS and Frequency of Anteverted Nares (%) (4 studies)

		173		quen				
	FAS	5	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	11	55	17	145	27.6%	1.88 [0.82, 4.33]	+=-	•
May et al 2013a	34	68	32	90	35.6%	1.81 [0.95, 3.44]	<b>+</b> ∎	•
May et al 2017	25	129	15	104	32.9%	1.43 [0.71, 2.87]		•
Viljoen et al 2005	8	64	0	146	3.9%	44.08 [2.50, 776.37]		- •
Total (95% CI)		316		485	100.0%	1.92 [1.07, 3.44]	◆	
Total events	78		64					
Heterogeneity: Tau <sup>2</sup> :	= 0.14; Ch	i² = 5.2	1, df = 3 (	(P = 0.1	6); I <sup>z</sup> = 42	2%		
Test for overall effect	: Z = 2.18	(P = 0.0	)3)	-			0.001 0.1 1 10 11 Control FAS	000

## Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Anteverted Nares (%) (4 studies)

•		~ -	-			O data Datia		O d d = D = ti =	Risk of Bias	
	pFA	5	Cont	IOI		Odds Ratio		Odds Ratio	KISK OF BIAS	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α	
May et al 2010 - Italian Cohort (FAS/pFAS)	9	39	20	179	23.7%	2.38 [0.99, 5.74]			?	
May et al 2007	8	18	17	145	19.5%	6.02 [2.09, 17.36]			•	
May et al 2013a	20	52	32	90	28.5%	1.13 [0.56, 2.29]		+	•	
May et al 2017	24	100	15	104	28.3%	1.87 [0.92, 3.83]		<b>⊢</b>	•	
Total (95% CI)		209		518	100.0%	2.16 [1.16, 4.02]		•		
Total events	61		84							
Heterogeneity: Tau <sup>2</sup> = 0.22; Chi <sup>2</sup> = 6.84, df =	3 (P = 0.0	08); I <sup>2</sup> =	56%				0.001		1000	
Test for overall effect: Z = 2.43 (P = 0.02)							0.001	Control pFAS	1000	

# ARND/Others and Frequency of Anteverted Nares (%) (2 studies)

	ARND/Ot	hers	Contr	ol		Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl A
May et al 2013a (ARND)	11	35	32	90	62.1%	0.83 [0.36, 1.91]	
May et al 2017 (ARND)	2	55	15	104	37.9%	0.22 [0.05, 1.02]	
Total (95% CI)		90		194	100.0%	0.51 [0.15, 1.76]	•
Total events	13		47				
Heterogeneity: Tau <sup>2</sup> = 0.4 <sup>2</sup> Test for overall effect: Z =			1 (P = 0.1	1 4); I² =	55%		0.001 0.1 1 10 1000 Control ARND/Others

Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005. May et al 2013a reports ARND and non-syndromal, used former.

# Outercanthal distance (mm) (m/SD)

	FAS	S/pFAS	5	C	ontrol		9	Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Foround et al 2012	78.98	0.71	35	81.11	0.35	49	100.0%	-3.98 [-4.74, -3.23]		•
Total (95% CI)			35			49	100.0%	-3.98 [-4.74, -3.23]	•	
Heterogeneity: Not ap	plicable								<u> </u>	
Test for overall effect:	Z=10.3	5 (P <	0.0000	01)					FAS/pFAS Control	

Risk of bias legend (A) Overall RoB

# ARND/Others and Outercanthal Distance (mm) (m/SD) (1 study)

	ARNI	D/Othe	rs	С	ontrol			Std. Mean Difference	Std. Mean Difference Risk of E
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI A
Foround et al 2012 (non-syndromal)	83.24	0.71	41	81.11	0.35	49	100.0%	3.88 [3.17, 4.59]	
Total (95% CI)			41			49	100.0%	3.88 [3.17, 4.59]	•
Heterogeneity: Not applicable Test for overall effect: $Z = 10.67$ (P < 0.	00001)								-4 -2 0 2 4 ARND/Others Control

Risk of bias legend (A) Overall RoB

*Notes*: All unmarked studies use dysmorphology assessment described by Hoyme 2005. Foround et al 2012 reported measures at 5yrs and 9yrs, used 5yrs in meta-analysis.

# Outercanthal Distance (Centile)

		F	ASD	and (	Duter	cantl	hal Dist	ance (Centile) (2	2 stu	udies)	
		FASD		0	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, Random, 95% CI	Α
Gomez et al 2020*	38.16	20.21	786	41.85	20.84	348	97.8%	-0.18 [-0.31, -0.05]			•
May et al 2021*	32.2	14.4	6	43.2	20.2	71	2.2%	-0.55 [-1.39, 0.29]			•
Total (95% CI)			792			419	100.0%	-0.19 [-0.31, -0.06]		•	
Heterogeneity: Tau² = Test for overall effect:			•	1 (P = 0	.40); I² =	= 0%			-4	-2 0 2 FASD Control	4

#### Risk of bias legend (A) Overall RoB

# FAS and Outercanthal Distance (Centile) (4 studies)

		FAS		0	Control			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019*	11.4	8.8	5	33.6	21.1	761	4.1%	-1.05 [-1.93, -0.17]		•
Gomez et al 2020*	17.72	12.54	305	41.85	20.84	348	86.1%	-1.38 [-1.55, -1.21]		•
May et al 2020a*	9	7.6	4	36.8	19.4	278	3.3%	-1.44 [-2.43, -0.44]		•
May et al 2020b*	18.8	14.7	8	34.6	20.2	413	6.5%	-0.78 [-1.49, -0.08]		•
Total (95% CI)			322			1800	100.0%	-1.33 [-1.51, -1.15]	•	
Heterogeneity: Tau² = 0. Test for overall effect: Z =				P = 0.38	l); <b> ²</b> = 2	%			-2 -1 0 1 2 FAS Control	1 2

#### Risk of bias legend (A) Overall RoB

# pFAS Outercanthal Distance (Centile) (4 studies)

			•					• • • •	•	
		pFAS		0	Control			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019*	27.5	24	44	33.6	21.1	761	27.2%	-0.29 [-0.59, 0.02]		•
Gomez et al 2020*	27.02	16.46	273	41.85	20.84	348	35.9%	-0.78 [-0.94, -0.61]	-	•
May et al 2020a*	22	16.2	22	36.8	19.4	278	19.8%	-0.77 [-1.21, -0.33]	_ <b>-</b> _	•
May et al 2020b*	24.4	15.1	16	34.6	20.2	413	17.1%	-0.51 [-1.01, -0.01]		•
Total (95% CI)			355			1800	100.0%	-0.60 [-0.87, -0.33]	•	
Heterogeneity: Tau <sup>2</sup> = 0.0	05; Chi <sup>z</sup>	= 8.35,	df = 3 (	P = 0.04	l); l <sup>2</sup> = 6	4%				<del></del>
Test for overall effect: Z =	•								-2 -1 U 1 pFAS Control	2

(A) Overall RoB

*Notes:* All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005.

# MANDIBULAR ARC

					N	1andi	bular A	rc (mm) (m/SD)		
			FA	SD an	d N	landi	bular A	Arc (mm) (m/SD)	(1 study)	
	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
May et al 2021*	24.9	1.4	6	26.1	1.5	71	100.0%	-0.80 [-1.64, 0.05]		•
Total (95% CI)			6			71	100.0%	-0.80 [-1.64, 0.05]	-	
Heterogeneity: Not ap	oplicable									
Test for overall effect:	Z=1.85	5 (P =	0.06)						-4 -2 0 2 FASD Control	4
Risk of bias legend										

(A) Overall RoB

# FAS and Mandibular Arc (mm) (m/SD) (6 studies)

	F	FAS		Co	ontro	I		Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
Chambers et al 2019*	24.4	2.1	5	26.3	1.3	761	10.6%	-1.45 [-2.34, -0.57]		•
May et al 2013	23.9	0.9	68	25.1	0.9	90	23.8%	-1.33 [-1.67, -0.98]	-	•
May et al 2017	24.1	1.3	129	25.2	1.5	104	26.3%	-0.79 [-1.06, -0.52]		•
May et al 2020a*	24.3	0.4	4	25.8	1.2	278	9.1%	-1.25 [-2.25, -0.26]	<b>_</b>	•
May et al 2020b*	24.1	1	8	25.6	1.4	413	14.0%	-1.07 [-1.78, -0.37]		•
May et al 2020c*	23.7	1.3	11	25.9	1.2	521	16.2%	-1.83 [-2.43, -1.22]		•
Total (95% CI)			225			2167	100.0%	-1.24 [-1.59, -0.88]	•	
Heterogeneity: Tau <sup>2</sup> = 0.	11; Chi²	= 13.	09, df=	= 5 (P =	0.02)	; <b>I</b> ² = 62	2%		<del>-                                    </del>	<u> </u>
Test for overall effect: Z =	= 6.82 (P	· < 0.۱	00001)	-		-			-4 -2 U 2 4 FAS Control	ł

Risk of bias legend (A) Overall RoB

					-			• • • • • • • • •			
	F F	FAS		Co	ontro			Std. Mean Difference	:	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Chambers et al 2019*	26	1.2	44	26.3	1.3	761	21.0%	-0.23 [-0.54, 0.07]			•
May et al 2013	24.7	1.2	52	25.1	0.9	90	18.0%	-0.39 [-0.73, -0.05]			•
May et al 2017	25.1	1	100	25.2	1.5	104	23.6%	-0.08 [-0.35, 0.20]		-	•
May et al 2020a*	25.6	1	22	25.8	1.2	278	13.1%	-0.17 [-0.60, 0.27]			•
May et al 2020b*	24.8	1.2	16	25.6	1.4	413	10.5%	-0.57 [-1.07, -0.07]			•
May et al 2020c*	25.1	0.8	23	25.9	1.2	521	13.8%	-0.67 [-1.09, -0.25]			•
Total (95% CI)			257			2167	100.0%	-0.31 [-0.49, -0.13]		•	
Heterogeneity: Tau² = 0. Test for overall effect: Z	•		•	5 (P = 0	.19);	l² = 339	%		-4	-2 0 2 pFAS Control	4

Risk of bias legend

(A) Overall RoB

	ARN	o/o	ther	s and	Ma	andik	oular A	rc (mm) (m/SD	) (6 studies)	
	P	FAS		Co	ontro	I	:	Std. Mean Difference	Std. Mean Difference R	isk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019* (ARND)	26	1.2	44	26.3	1.3	761	21.0%	-0.23 [-0.54, 0.07]		•
May et al 2013 (ARND)	24.7	1.2	52	25.1	0.9	90	18.0%	-0.39 [-0.73, -0.05]		•
May et al 2017 (ARND)	25.1	1	100	25.2	1.5	104	23.6%	-0.08 [-0.35, 0.20]	+ (	•
May et al 2020a* (ARND)	25.6	1	22	25.8	1.2	278	13.1%	-0.17 [-0.60, 0.27]		•
May et al 2020b* (ARND)	24.8	1.2	16	25.6	1.4	413	10.5%	-0.57 [-1.07, -0.07]		•
May et al 2020c* (ARND)	25.1	0.8	23	25.9	1.2	521	13.8%	-0.67 [-1.09, -0.25]		
Total (95% CI)			257			2167	100.0%	-0.31 [-0.49, -0.13]	•	
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup>	= 7.50, c	∦f = 5	(P = 0.1)	19); I <sup>z</sup> =	33%					
Test for overall effect: Z = 3.36 (F	° = 0.000	18)							pFAS Control	

Risk of bias legend

(A) Overall RoB

Notes: \* indicates dysmorphology assessment other than Hoyme 2005.

Mandibular Arc (z-score)

#### FAS and Mandibular Arc (z-score) (1 study) Control Std. Mean Difference Std. Mean Difference Risk of Bias FAS IV, Random, 95% CI SD Total SD Total Weight Study or Subgroup Mean Mean IV, Random, 95% CI Α Moore et al 2002\* -0.4264 1.4436 40 1.4977 1.3039 31 100.0% -1.37 [-1.90, -0.85] Total (95% CI) 40 31 100.0% -1.37 [-1.90, -0.85] ⊢ -4 Heterogeneity: Not applicable 4 -5 Ó Ĵ Test for overall effect: Z = 5.15 (P < 0.00001) FAS Control

Risk of bias legend (A) Overall RoB

# pFAS and Mandibular Arc (z-score) (1 study)

		pFAS	•	0	Control			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Moore et al 2002*	1.0596	1.5078	59	1.4977	1.3039	31	100.0%	-0.44 [-1.04, 0.16]		•
<b>Total (95% CI)</b> Heterogeneity: Not ap Test for overall effect:	•	(P = 0.15)	<b>59</b> )			31	100.0%	-0.44 [-1.04, 0.16]	-4 -2 0 2 4 pFAS Control	

Risk of bias legend

(A) Overall RoB

Notes: Moore et al 2002 used z-score Farkas 1981 norms.

# MAXILLARY ARC

					I		· · ·	c (cm) (m/SD)		
	E	ASD	F		ana			rc (cm) (m/SD) (1 Std. Mean Difference	study) Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	Α
May et al 2021*	24.1	0.9	6	25	1.3	71	100.0%	-0.70 [-1.54, 0.14]		•
Total (95% CI)			6			71	100.0%	-0.70 [-1.54, 0.14]	-	
Heterogeneity: Not ap Test for overall effect:			0.10)						-4 -2 0 2 4 FASD Control	

Risk of bias legend (A) Overall RoB

# FAS and Maxillary Arc (cm) (m/SD) (6 studies)

	1	FAS		Co	ontro	1		Std. Mean Difference	Std. Mean D	ifference	Risk of Bia
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Randon	n, 95% Cl	Α
Chambers et al 2019*	23.6	1.3	5	25.1	1.2	761	11.8%	-1.25 [-2.13, -0.37]	<b>_</b>		•
May et al 2013	23.2	0.8	68	23.8	2.6	90	22.8%	-0.29 [-0.61, 0.02]	-=-		•
May et al 2017	23.1	1.2	129	24.1	1.3	104	23.8%	-0.80 [-1.07, -0.53]	-		•
May et al 2020a*	23.7	0.4	4	24.7	1.1	278	10.3%	-0.91 [-1.90, 0.08]			•
May et al 2020b*	23	0.6	8	24.6	1.2	413	14.7%	-1.34 [-2.04, -0.63]			•
May et al 2020c*	23.3	1.1	11	24.8	1	521	16.7%	-1.49 [-2.10, -0.89]			•
Total (95% CI)			225			2167	100.0%	-0.94 [-1.35, -0.54]	•		
Heterogeneity: Tau <sup>2</sup> = 0.	16; Chi <b></b>	= 17.	.96, df=	= 5 (P =	0.003	3); I <b>2</b> = 7	2%	ŀ	ŀ <u>, t</u>	<u> </u>	
Test for overall effect: Z:	= 4.57 (P	< 0.1	00001)					-	-4 -2 U	Control	4
	-								FAS	Control	

pFAS and Maxillary Arc (cm) (m/SD) (6 studies)

	p	FAS		Co	ontro	I I		Std. Mean Difference	Std. Mean Difference	<b>Risk of Bias</b>
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019*	24.8	1.1	44	25.1	1.2	761	20.9%	-0.25 [-0.55, 0.05]	-=-	•
May et al 2013	23.8	1	52	23.8	2.6	90	18.2%	0.00 [-0.34, 0.34]	+	•
May et al 2017	23.9	0.9	100	24.1	1.3	104	23.2%	-0.18 [-0.45, 0.10]	-=+	•
May et al 2020a*	24.4	0.9	22	24.7	1.1	278	13.2%	-0.28 [-0.71, 0.16]	+	•
May et al 2020b*	24	1.1	16	24.6	1.2	413	10.7%	-0.50 [-1.00, -0.00]		•
May et al 2020c*	24.1	0.8	23	24.8	1	521	13.8%	-0.70 [-1.12, -0.28]		•
Total (95% CI)			257			2167	100.0%	-0.28 [-0.47, -0.10]	•	
Heterogeneity: Tau² = 0. Test for overall effect: Z =				5 (P = 0	.17);	I² = 369	6		-4 -2 0 2 pFAS Control	4

Risk of bias legend

(A) Overall RoB

# ARND/Others and Maxillary Arc (cm) (m/SD) (6 studies)

	ARND	/Othe	rs	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% Cl	Α
Chambers et al 2019* (ARND)	25.3	1.3	44	25.1	1.2	761	19.7%	0.17 [-0.14, 0.47]		•
May et al 2013 (ARND)	23.5	1.1	35	23.8	2.6	90	17.7%	-0.13 [-0.52, 0.26]		•
May et al 2017 (ARND)	23.6	0.9	55	24.1	1.3	104	19.1%	-0.42 [-0.75, -0.09]		•
May et al 2020a* (ARND)	25.4	1.4	12	24.7	1.1	278	13.5%	0.63 [0.05, 1.21]		•
May et al 2020b* (ARND)	24	1.3	25	24.6	1.2	413	17.4%	-0.50 [-0.90, -0.09]		•
May et al 2020c* (ARND)	24.2	1.2	10	24.8	1	521	12.6%	-0.60 [-1.22, 0.03]		
Total (95% CI)			181			2167	100.0%	-0.15 [-0.47, 0.18]	•	
Heterogeneity: Tau² = 0.12; Chi² :	= 18.43, (	df = 5	(P = 0.1	002); I² :	= 739	6				
Test for overall effect: Z = 0.89 (P	= 0.37)								ARND/Others Control	т

Risk of bias legend (A) Overall RoB

Notes: All unmarked studies use dysmorphology assessment described by Hoyme 2005. \* indicates dysmorphology assessment other than Hoyme 2005.

# Maxillary Arc (z-score)

			I	FAS ar	nd Max	xillar	y Arc (	z-score) (1 stud	ly)			
		FAS		0	Control			Mean Difference		Mean Differe	nce	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IN	/, Random, 9	5% CI	Α
Moore et al 2002*	-1.0573	1.2546	40	0.9918	1.4112	31	100.0%	-2.05 [-2.68, -1.42]	-	-		•
Total (95% CI)			40			31	100.0%	-2.05 [-2.68, -1.42]	-	•		
Heterogeneity: Not a	nnlicahle								H		<u> </u>	i
Therefore the transferred to the termination of terminatio of	ppricable											
Test for overall effect		P < 0.000	001)						-4 -2	FAS Cor	1trol	4
		P < 0.000	r	FAS a	nd Ma	villa	ry Arc	(7-score) (1 stu		-	1trol	4
Test for overall effect Risk of bias legend	:Z=6.37(		r			ixilla	ry Arc	(z-score) (1 stu	dy)	FAS Cor		4 Pick of Pice
Test for overall effect <u>Risk of bias legend</u> (A) Overall RoB	:Z=6.37(	P < 0.000 pFAS SD	r		nd Ma Control	<b>xilla</b> Total		Mean Difference	dy)	-	nce	4 Risk of Bias A
Test for overall effect Risk of bias legend	: Z = 6.37 (	pFAS	p Total	C Mean	ontrol			• • •	dy)	FAS Cor	nce	

-4

-2

4

ż

pFAS Control

Total (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 1.17 (P = 0.24)

Risk of bias legend (A) Overall RoB

Notes: Moore et al 2002 use norms by Farkas 1981.

		<b>Other Minor Non-Facial Featur</b>	es
Study Type	Outcome	Data	# of studies
	Heart Problems	Heart Defect(%)	2 studies: 1 moderate PAE, 1 very heavy
			PAE and 1 confirmed unquantifiable PAE
		Heart Murmur (%)	<b>1 study</b> with moderate PAE and very heavy
			PAE
	Hypertrichosis	Hypertrichosis (%)	0 studies
	Hypoplastic Nails	Hypoplastic Nails (%)	<b>1 study</b> with confirmed unquantifiable PAE
Exposure	Camptodactyly	Camptodactyly (%)	<b>1 study</b> with moderate PAE and very heavy PAE
Studies	"Railroad Track" Ears	"Railroad Track" Ears (%)	<b>1 study</b> with moderate PAE and very heavy PAE
	Decreased Joint	Limited/Decreased Elbow	1 study with moderate PAE and very heavy
	Supination	Supination (%)	PAE
	Altered Palmar Crease	Altered Palmar Crease (%)	<b>2 studies:</b> 1 moderate, 1 very heavy PAE and 1
			confirmed unquantifiable PAE
	5th Finger	5th Finger Clinodactyly (%)	<b>1 study</b> with moderate PAE and very heavy
	Clinodactyly		PAE
	Heart Problems	Heart Defect (%)	<b>5 studies:</b> 1x FASD, 4x FAS, 4x pFAS, 3x ARND/Others
		Heart Murmur (%)	<b>7 studies:</b> 1x FASD 5x FAS, 5x pFAS, 2x ARND/Others
	Hypertrichosis	Hypertrichosis (%)	<b>4 studies:</b> 1x FASD, 3x FAS, 1x pFAS
	Hypoplastic Nails	Hypoplastic Nails (%)	5 studies: 1x FASD, 4x FAS, 4x pFAS, 3x
			ARND/Others
Diagnosed	Camptodactyly	Camptodactyly (%)	<b>9 studies:</b> 1x FASD, 6x FAS, 6x pFAS, 3x ARND/Others
Studies	"Railroad Track" Ears	"Railroad Track" Ears (%)	<b>5 studies:</b> 1x FASD, 4x FAS, 4x pFAS, 2x ARND/Others
	'Other' Ear	'Other' Ear Abnormalities	2x studies: 1x FASD and 1x FAS, 1x pFAS, 1x
	Abnormalities	(%)	ARND/Others
	Decreased Joint	Limited/Decreased Elbow	5 studies: 1x FASD, 4x FAS, 3x pFAS, 2x
	Supination	Supination (%)	ARND/Others
	Altered Palmar Crease	Altered Palmar Crease (%)	<b>9 studies:</b> 2x FASD, 6x FAS, 6x pFAS, 4x ARND/Others
	5th Finger Clinodactyly	5th Finger Clinodactyly (%)	8 studies: 2x FASD, 5x FAS, 5x pFAS, 2x ARND

# Summary of available outcomes for other minor non-facial features

# GRADE ratings for other minor features

		Cert	ainty assessn	nent		Nº of pa	atients	Ef	ifect	
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerati ons	ΡΑΕ	Control	Relative (95% Cl)	Absolute (95% Cl)	Certainty
EXPOSUR	E STUDIE	S	-	-						-
HEART PR	OBLEMS	;								
Heart Def	ect (%)									
Moderate	PAE									
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	4/45	5/253	<b>OR 4.84</b> (1.25 to 18.77)	-	
Very Heav	/y PAE		•						•	•
	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	4/19 (21.1%)	5/253 (2.0%)	<b>OR 13.23</b> (3.22 to 54.41)	<b>191 more per</b> <b>1,000</b> (from 41 more to 503 more)	
Confirme	d Unqua	ntifiable					1	1	1	-
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	12	12	<b>OR 5.50</b> (0.51 to 59.01)	-	⊕○○○ Very low
Heart Mu	rmur (%)									
Moderate	PAE									
1	seriousª	not serious	not serious	serious <sup>e, f</sup>	none	9/45	19/253	<b>OR 3.08</b> (1.29 to 7.33)	-	
Very Heav	vy PAE									
1	seriousª	not serious	not serious	serious <sup>e,f</sup>	none	9/19 (47.4%)	19/253 (7.5%)	<b>OR 11.08</b> (4.02 to 30.58)	-	⊕⊕⊖⊖ Low
HYPERTRI	CHOSIS	(0 STUDIES)	•						•	
HYPOPLA	STIC NAI	LS								
Hypoplas	tic Nails	(%)								
Confirme	d Unqua	ntifiable								
		not serious	not serious	very serious <sup>d,e,f</sup>	none	5/12 (41.7%)	0/12 (0.0%)	<b>OR 18.33</b> (0.88 to 380.70)	<b>0 fewer per</b> <b>1,000</b> (from 0 fewer to 0 fewer)	⊕○○○ Very low
CAMPTO										
Camptoda		)								
Moderate	PAE			•				•		
	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/45	4/253	<b>OR 1.41</b> (0.15 to 12.96)		⊕○○○ Very low
Very Heav	vy PAE		-							
1	seriousª	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/19 (5.3%)	2/253 (1.6%)	OR 3.46 (0.37 to 32.58)		⊕○○○ Very low
EAR ABNO	ORMALIT	IES						· · ·	•	
Railroad t	rack ears	s (%)								
Moderate	PAE									
1	seriousª	not serious	not serious	very serious <sup>d,e,f</sup>	none	4/45	19/253	<b>OR 1.20</b> (0.39 to 3.71)		⊕⊖⊖C Very low
Very Hea	vy PAE						-		-	•
-	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/19	19/253	<b>OR 0.68</b> (0.09 to 5.41)		⊕⊖⊖C Very low

Linniea/	Decreases									
Moderat		d Elbow Supina	ation (%)							
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	3/45	1/253	<b>OR 18.00</b> (1.83 to		⊕○○C Very low
Very Hea	ανν ΡΔΕ							177.15)		
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/19 (5.3%)	1/253 (0.4%)	<b>OR 14.00</b> (0.84 to 233.18)	<b>49 more per</b> <b>1,000</b> (from 1 fewer to 477 more)	⊕OOC Very low
ALTERED	PALMAR	CREASE (%)		. <u> </u>		1	1		· ·	
Altered I	Palmar Cr	ease (%)								
Moderat	te PAE						_			
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	6/45	28/253	OR 1.24 (0.48 to 3.18)		⊕○○C Very low
Very Hea	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	4/19 (21.1%)	28/253 (11.1%)	<b>OR 2.14</b> (0.66 to 6.91)	<b>100 more per</b> <b>1,000</b> (from 35 fewer to 352)	⊕○○C Very low
Confirm	ed Unqua	ntifiable	_							
1	seriousª	not serious	not serious	very serious <sup>d,e,f</sup>	none	3/12	0/12	<b>OR 9.21</b> (0.42 to 200.59)	-	⊕○○C Very low
Moderat 1	te PAE serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	1/45	33/253	<b>OR 0.15</b> (0.02 to 1.14)	-	
1	serious <sup>a</sup>	not serious	not serious		none	1/45	33/253	<b>OR 0.15</b> (0.02 to 1.14)	-	
1	serious <sup>a</sup>		not serious		none	2/19	34/253	to 1.14)	- <b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low
1 Very Hea 1	serious <sup>a</sup> avy PAE	not serious		serious <sup>d,e,f</sup> very		2/19	34/253	to 1.14)	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213	Very low
Very Hea 1 DIAGNO CARDIAC	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI	not serious		serious <sup>d,e,f</sup> very		2/19	34/253	to 1.14)	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213	
1 Very Hea 1 DIAGNO CARDIAC Heart De	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI	not serious		serious <sup>d,e,f</sup> very		2/19	34/253	to 1.14)	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213	Very low
1 Very Hea 1 DIAGNO CARDIAC	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI	not serious		serious <sup>d,e,f</sup> very		2/19 (10.5%)	34/253	to 1.14)	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low
1 I DIAGNO CARDIAC Heart De FASD 1	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI efect (%)	not serious NES MS	not serious	serious <sup>d,e,f</sup> very serious <sup>d,e,f</sup>	none	2/19 (10.5%)	34/253 (13.4%)	to 1.14) OR 0.76 (0.17 to 3.43)	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low
1 I DIAGNO CARDIAC Heart De FASD 1	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI efect (%)	not serious NES MS	not serious	serious <sup>d,e,f</sup> very serious <sup>d,e,f</sup>	none	2/19 (10.5%)	34/253 (13.4%)	to 1.14) OR 0.76 (0.17 to 3.43) not estimable OR 8.03	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low ⊕○○○ Very low N/A
1 Very Hea 1 DIAGNO CARDIAC Heart De FASD 1 FAS	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI efect (%) serious <sup>a</sup>	not serious	not serious not serious	serious <sup>d,e,f</sup> very serious <sup>d,e,f</sup> N/A very	none	2/19 (10.5%) 0/22 (0.0%) 2/139	34/253 (13.4%) 0/67 (0.0%) 5/1517	to 1.14) OR 0.76 (0.17 to 3.43) not estimable OR 8.03 (0.43 to	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low
1 Very Hea 1 DIAGNO CARDIAC Heart De FASD 1 FAS 4	serious <sup>a</sup> avy PAE serious <sup>a</sup> SED STUD C PROBLEI efect (%) serious <sup>a</sup>	not serious	not serious not serious	serious <sup>d,e,f</sup> very serious <sup>d,e,f</sup> N/A very	none	2/19 (10.5%) 0/22 (0.0%) 2/139	34/253 (13.4%) 0/67 (0.0%) 5/1517	to 1.14) <b>OR 0.76</b> (0.17 to 3.43) not estimable <b>OR 8.03</b> (0.43 to 150.80) <b>OR 5.26</b> (0.59 to	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low ⊕○○○ Very low N/A
1 Very Hea 1 DIAGNO CARDIAC Heart De FASD 1 FAS 4 pFAS	serious <sup>a</sup> serious <sup>a</sup> serious <sup>a</sup> SED STUD C PROBLEI efect (%) serious <sup>a</sup> serious <sup>a</sup>	not serious MES MS not serious serious <sup>b</sup>	not serious not serious not serious	serious <sup>d,e,f</sup> very serious <sup>d,e,f</sup> N/A very serious <sup>d,e,f</sup>	none	2/19 (10.5%) 0/22 (0.0%) 2/139 (1.4%) 2/137	34/253 (13.4%) 0/67 (0.0%) 5/1517 (0.32%) 5/1517	to 1.14) OR 0.76 (0.17 to 3.43) not estimable OR 8.03 (0.43 to 150.80) OR 5.26	<b>29 fewer per</b> <b>1,000</b> (from 109 fewer to 213 more)	Very low ⊕○○○ Very low N/A ⊕○○○ Very low

FASD										57
1	serious <sup>a</sup>	not serious	not serious	very	none	0/22	1/67	OR 0.99	0 fewer per	000
-	Serious			serious <sup>d,e,f</sup>	lione	(0.0%)	(1.5%)	(0.04 to 25.06)	fewer to 260 more)	Very low
FAS										
5	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	26/199 (13%)	27/1332 (2.02%)	<b>OR 4.95</b> (2.32 to 10.53)	-	⊕⊕⊖⊖ Low
pFAS			•			-				
5	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	14/172 (8.1%)	29/1365 (2.1%)	<b>OR 3.12</b> (1.53 to 6.38)	-	⊕⊖⊖⊖ Very low
ARND/O	thers									
2	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	4/79 (5.1%)	20/851 (2.4%)	<b>OR 1.29</b> (0.40 to 4.20)	<b>7 more per</b> <b>1,000</b> (from 14 fewer to 68 more)	⊕○○○ Very low
HYPERT	RICHOSIS									
Hypertri	chosis (%)									
FASD										
1	serious <sup>a</sup>	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	not estimable	-	N/A
<b>FAS</b> (one	e study nor	n-estimable)	-			-				
3	seriousª	not serious	not serious	serious <sup>e,f</sup>	none	3/126 (2.3%)	4/481 (0.83%)	<b>OR 6.99</b> (1.27 to 38.45)	-	⊕⊕⊖C Low
pFAS				11				/		
1	seriousª	not serious	serious <sup>c</sup>	very serious <sup>d,e,f</sup>	none	1/18 (5.6%)	0/145 (0.0%)	OR 24.94 (0.98 to 636.12)	-	⊕⊖⊖⊖ Very low
HYPOPL	ASIC NAILS	5 (%)					1	,		
Hypopla	stic Nails	(%)								
FASD										
1	serious <sup>a</sup>	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	not estimable	-	N/A
FAS			•				•			
4	seriousª	not serious	not serious	serious <sup>e,f</sup>	none	10/135 (7.4%)	6/926 (0.65%)	<b>OR 5.50</b> (1.82 to 16.68)	-	⊕⊕⊖⊖ Low
pFAS							•			•
4	seriousª	not serious	not serious	serious <sup>e,f</sup>	none	5/108 (4.6%)	6/926 (0.65%)	<b>OR 5.42</b> (1.59 to 18.41)	-	⊕⊕⊖⊖ Low
ARND/O	thers			. I		•		,		
3	seriousª	not serious	not serious	very serious <sup>d,e,f</sup>	none	2/72 (3.3%)	4/781 (0.8%)	<b>OR 2.82</b> (0.53 to 15.07)	<b>14 more per</b> <b>1,000</b> (from 4 fewer to 1000 more)	⊕○○○ Very low
САМРТС	DDACTYLY								, ,	
Campto	dactyly (%	)								
FASD										
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	5/22 (22.7%)	5/67 (7.5%)	OR 3.65	<b>153 more per</b> <b>1,000</b> (from 4	⊕⊖⊖⊖ Very low

										58
								(0.94 to	fewer to 457	
								14.08)	more)	
FAS			•							•
6	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	85/346 (24.56%)	49/1196 (4.1%)	<b>OR 5.88</b> (3.75 to 9.21)	-	⊕○○○ Very low
pFAS										
6	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	27/239 (11.29%)	62/1229 (5.04%)	<b>OR 2.31</b> (1.08 to 4.92)	-	⊕⊕⊖⊖ Low
ARND/O	thers		-			• • •	• • •	•••		
3	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>d,f</sup>	none	8/100 (8.0%)	24/715 (3.4%)	<b>OR 1.66</b> (0.68 to 4.01)	<b>21 more per</b> <b>1,000</b> (from 10 fewer to 89 more)	⊕○○○ Very low
	NORMALI									
"Railroa	d Track" E	Ears (%)								
FASD										
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	5/22 (22.7%)	4/67 (6.0%)	<b>OR 4.63</b> (1.12 to 19.16)	<b>167 more per</b> <b>1,000</b> (from 7 more to 489 more)	⊕○○○ Very low
FAS										
4	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	89/316 (28.16%)	24/503 (11.8%)	<b>OR 5.47</b> (2.75 to 10.87)	-	⊕○○○ Very low
pFAS								-		
4	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>f</sup>	none	31/209 (14.8%)	35/518 (6.76%)	<b>OR 1.94</b> (1.07 to 3.53)	-	⊕⊖⊖⊖ Very low
ARND/O	thers		-				•	•		
2	serious <sup>a</sup>		serious <sup>c</sup>	serious <sup>d,f</sup>	none	9/90 (10.0%)	19/194 (9.8%)	<b>OR 0.96</b> (0.41 to 2.23)	<b>4 fewer per</b> <b>1,000</b> (from 55 fewer to 97 more)	⊕○○○ Very low
'OTHER'	EAR ABN	ORMALITIES								
Low set	ears (%)									
FASD										
2	serious <sup>a</sup>	serious <sup>b</sup>	not serious	very serious <sup>d,e,f</sup>	none	9/119 (7.6%)	16/788 (2.0%)	<b>OR 2.78</b> (0.34 to 22.87)	<b>34 more per</b> <b>1,000</b> (from 13 fewer to 301 more)	⊕○○○ Very low
DECREA	SED JOINT	<b>SUPINATION</b>								
Limited/	/Decrease	d Elbow Supina	ation (%)							
FASD										
1	serious <sup>a</sup>	not serious	not serious	very serious <sup>d,e,f</sup>	none	3/22 (13.6%)	2/67 (3.0%)	<b>OR 5.13</b> (0.80 to 32.99)	<b>106 more per</b> <b>1,000</b> (from 6 fewer to 474 more)	⊕○○○ Very low
FAS	<u> </u>		-		-	-	-		- · ·	-
4	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	8/192 (4.17%)	25/1142 (2.19%)	<b>OR 4.67</b> (1.57 to 13.95)	-	⊕○○○ Very low
pFAS	<u> </u>		-		-	-	-	· · ·		-
3	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>e,f</sup>	none	7/114 (6.14%)	23/996 (2.31%)	<b>OR 4.15</b> (1.60 to 10.79)	-	⊕○○○ Very low
ARND/O	others		-	·	-		<u> </u>			-

/851 <b>OR 0.54</b> .6%) (0.06 to 4.52)	<b>12 fewer per</b> <b>1,000</b> (from 24	⊕○○○ Very low
.6%) (0.06 to 4.52)		Very low
		v ci y 10 w
	fewer to 81	
	more)	
·		
4/94 OR 3.45	228 more per	$\oplus \oplus \bigcirc \bigcirc$
4.9%) (1.34 to 8.88)	<b>1,000</b> (from 41	Low
	to 460 more)	
2/176 OR 3.29	-	$\oplus O O O$
7.4%) (2.16 to 5.00)		Very low
3/180 OR 2.00	-	$\oplus \oplus \bigcirc \bigcirc$
8.2%) (1.25 to 3.19)		Low
/1476 OR 1.69	29 more per	$\oplus \oplus \bigcirc \bigcirc$
		Low
9/94 OR 1.50	73 more per	$\oplus \oplus \bigcirc \bigcirc$
-	-	Low
I		
0/733 OR 1.15	-	000
47%) (0.81 to 1.63)		Very low
2/766 OR 2.08	-	$\oplus \oplus \bigcirc \bigcirc$
5.8%) (1.24 to 3.48)		Low
5/252 OR 0.81	50 fewer per	$\oplus \bigcirc \bigcirc \bigcirc$
-,		-
1.7%) (0.27 to 2.50)	1,000	Very low
	<b>1,000</b> (from 255	Very low
	-	Very low
	.9%)       (1.34 to 8.88)         /176       OR 3.29         .4%)       (2.16 to 5.00)         /180       OR 2.00         .2%)       (1.25 to 3.19)         1476       OR 1.69         6%)       (1.00 to 2.86)         /94       OR 1.50         .2%)       (0.58 to 3.89)         /733       OR 1.15         47%)       (0.81 to 1.63)         /766       OR 2.08         .8%)       (1.24 to 3.48)	/94       OR 3.45       228 more per         .9%)       (1.34 to 8.88)       1,000 (from 41 to 460 more)         /176       OR 3.29       -         .4%)       (2.16 to 5.00)       -         /180       OR 2.00       -         .2%)       (1.25 to 3.19)       -         1476       OR 1.69       29 more per         1,000 (from 0 fewer to 75 more)       1,000 (from 0 fewer to 75 more)         /94       OR 1.50       73 more per         .2%)       (0.58 to 3.89)       1,000 (from 74 fewer to 294 more)         /733       OR 1.15       -         /733       OR 1.63)       -         /766       OR 2.08       -         .8%)       (1.24 to 3.48)       -

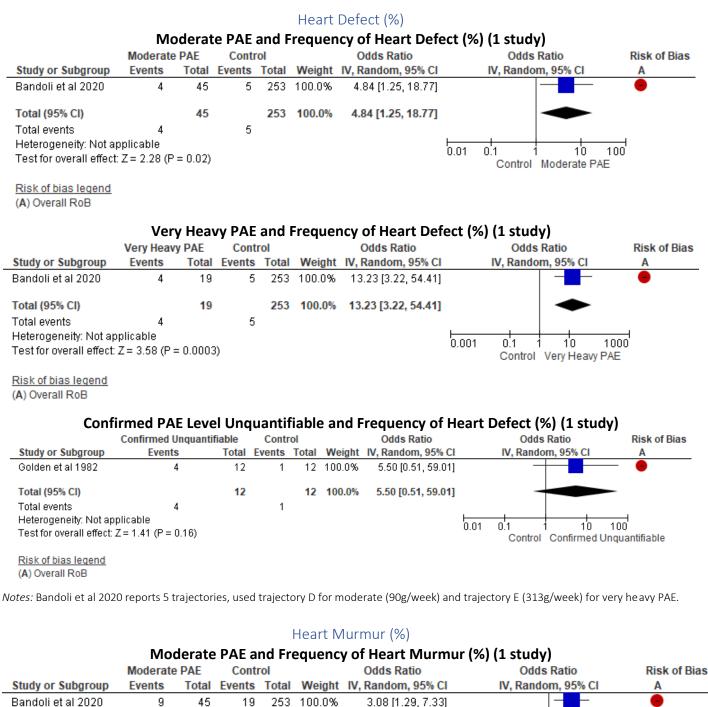
Notes: CI: confidence interval; MD: mean difference; SMD: standard mean difference; OR: odds ratio.

**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.

# Meta-analyses for minor non-facial features

# **Exposure Studies**

# CARDIAC PROBLEMS



Danaon et al 2020	5	40	10	200	100.070	5.00 [1.25, 1.55]		
Total (95% CI)		45		253	100.0%	3.08 [1.29, 7.33]		
Total events	9		19					
Heterogeneity: Not applical Test for overall effect: Z = 2		0.01)					L.01	0.1

Risk of bias legend (A) Overall RoB 10

Control Moderate PAE

1

100

	Very I	Heavy	/ PAE a	ind Fi	requen	cy of Heart Mur	mur (%) (1 study)	
	Very Heavy	PAE	Cont	rol		Odds Ratio	Odds Ratio	<b>Risk of Bias</b>
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	9	19	19	253	100.0%	11.08 [4.02, 30.58]		•
Total (95% CI)		19		253	100.0%	11.08 [4.02, 30.58]	•	
Total events	9		19					
Heterogeneity: Not a	pplicable							<u>_</u>
Test for overall effect	: Z= 4.65 (P <	0.0000	1)				0.001 0.1 1 10 100 Control Very Heavy PAE	
Risk of bias legend								
(A) Overall RoB								

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

## **HYPERTRICHOSIS (O STUDIES)**

#### HYPOPLASTIC NAILS

Co	nfirmed Unqua	ntifiable	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Golden et al 1982	5	12	0	12	100.0%	18.33 [0.88, 380.70]		- 🔸
Total (95% CI)		12		12	100.0%	18.33 [0.88, 380.70]		-
Total events	5		0					
Heterogeneity: Not applica	able					<u> </u>		
Test for overall effect: Z = 1	I.88 (P = 0.06)					0.0	01 0.1 1 10 Control Confirmed U	000 nguantifiable

(A) Overall RoB

## CAMPTODACTYLY

#### Camptodactyly (%) Moderate PAE and Frequency of Camptodactyly (%) (1 study) Moderate 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 Α Bandoli et al 2020 1 45 4 253 100.0% 1.41 [0.15, 12.96] Total (95% CI) 253 100.0% 45 1.41 [0.15, 12.96] Total events 1 4 Heterogeneity: Not applicable 0.01 0.1 10 100 1 Test for overall effect: Z = 0.31 (P = 0.76) Control Moderate PAE Risk of bias legend (A) Overall RoB Very Heavy PAE and Frequency of Camptodactyly (%) (1 study) Very Heavy PAE Control Odds Ratio Odds Ratio Risk of Bias IV, Random, 95% CI Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Bandoli et al 2020 19 100.0% 3.46 [0.37, 32.58] 1 4 253 Total (95% CI) 19 100.0% 3.46 [0.37, 32.58] 253 Total events 4 1 Heterogeneity: Not applicable 0.001 0.1 10 1000 Test for overall effect: Z = 1.08 (P = 0.28) Control Very Heavy PAE Risk of bias legend

(A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

# Railroad Track ears (%)

	Mode	rate P	AE and	d Freq	Juency	of railroad track	ears (%) (1 study)	
	Moderate	PAE	Contr	ol		Odds Ratio	Odds Ratio Risk of Bias	)
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl A	_
Bandoli et al 2020	4	45	19	253	100.0%	1.20 [0.39, 3.71]		
Total (95% CI)		45		253	100.0%	1.20 [0.39, 3.71]	<b>•</b>	
Total events	4		19					
Heterogeneity: Not ap	•						0.01 0.1 1 10 100	
Test for overall effect:	Z = 0.32 (P	= 0.75)					Control Moderate PAE	

# Risk of bias legend

(A) Overall RoB

# Very Heavy PAE and Frequency of railroad track ears (%) (1 study)

		,				y or rainoad ne		
	Very Heav	y PAE	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	1	19	19	253	100.0%	0.68 [0.09, 5.41]		•
Total (95% CI)		19		253	100.0%	0.68 [0.09, 5.41]		
Total events	1		19					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z=0.36 (P:	= 0.72)					Control Very Heavy PAE	
Risk of bias legend								
(A) Overall RoB								

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

# **DECREASED JOINT SUPINATIONS**

# Limited Elbow Supinations (%)

#### Moderate PAE and Frequency of Limited Elbow Supinations (%) (1 study) Moderate PAE Control Odds Ratio Odds Ratio Risk of Bias Study or Subgroup Events Total Events Total Weight IV, Random, 95% Cl IV, Random, 95% Cl 253 100.0% 18.00 [1.83, 177.15] Bandoli et al 2020 3 45 1 Total (95% CI) 45 253 100.0% 18.00 [1.83, 177.15] Total events 3 1 Heterogeneity: Not applicable 0.01 10 100 0.1 Test for overall effect: Z = 2.48 (P = 0.01) Control Moderate PAE

Risk of bias legend (A) Overall RoB

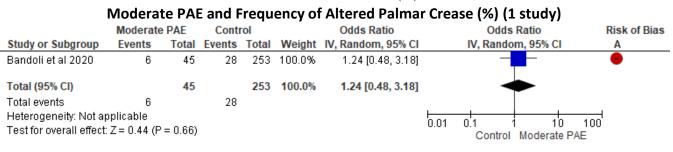
## Very Heavy PAE and Frequency of Limited Elbow Supinations (%) (1 study)

	Very Heav	y PAE	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Bandoli et al 2020	1	19	1	253	100.0%	14.00 [0.84, 233.18]			
Total (95% CI)		19		253	100.0%	14.00 [0.84, 233.18]			-
Total events	1		1						
Heterogeneity: Not a	pplicable						0.001		1000
Test for overall effect	:: Z = 1.84 (P =	= 0.07)					0.001	0.1 1 10 Control Very Heavy F	

Risk of bias legend (A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

### Altered Palmar Crease (%)



#### Risk of bias legend (A) Overall RoB

# Very Heavy PAE and Frequency of Altered Palmar Crease (%) (1 study)

•	i ci y i i cu	• • • • • •			<b>ciic</b> , <b>c</b>			
	Very Heav	y PAE	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	4	19	28	253	100.0%	2.14 [0.66, 6.91]		•
Total (95% CI)		19		253	100.0%	2.14 [0.66, 6.91]	•	
Total events	4		28					
Heterogeneity: Not ap	oplicable							
Test for overall effect:	Z=1.28 (P:	= 0.20)					Control Very Heavy PAE	

#### Risk of bias legend

#### (A) Overall RoB

# Confirmed PAE Level Unquantifiable and Frequency of Altered Palmar Crease (%) (1 study)

	Confirmed Unquan	tifiable	Contr	ol		Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Golden et al 1982	3	12	0	12	100.0%	9.21 [0.42, 200.59]	
Total (95% CI)		12		12	100.0%	9.21 [0.42, 200.59]	
Total events	3		0				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 1.41 (P = 0.16)						Control Confirmed Unquantifiable

#### Risk of bias legend

(A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

#### 5<sup>th</sup> FINGER CLINODACTYLY

Study or Subgroup         Events         Total         Events         Total         Weight         IV, Random, 95% Cl         IV, Random, 95% Cl         A           Bandoli et al 2020         1         45         33         253         100.0%         0.15 [0.02, 1.14]         Image: Cl         Image: Cl         Image: Cl         A           Total (95% Cl)         45         253         100.0%         0.15 [0.02, 1.14]         Image: Cl         Image: Cl         Image: Cl         A           Total (95% Cl)         45         253         100.0%         0.15 [0.02, 1.14]         Image: Cl         Ima		Moderate	PAE	Contr	•		of 5 <sup>th</sup> Finger Clino Odds Ratio	Odds Ratio	Risk of Bia
Total (95% CI) 45 253 100.0% 0.15 [0.02, 1.14]						Weight			
	Bandoli et al 2020	1	45	33	253	100.0%	0.15 [0.02, 1.14]		•
Total events 1 33	Total (95% CI)		45		253	100.0%	0.15 [0.02, 1.14]		
	Total events	1		33					
Heterogeneity: Not applicable 0.01 0.1 1 10 100	Heterogeneity: Not app	licable							

#### Risk of bias legend (A) Overall RoB

# Very Heavy PAE and Frequency of 5<sup>th</sup> Finger Clinodactyly (%) (1 study)

						0		
	Very Heav	y PAE	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Bandoli et al 2020	2	19	34	253	100.0%	0.76 [0.17, 3.43]		•
Total (95% CI)		19		253	100.0%	0.76 [0.17, 3.43]	-	
Total events	2		34					
Heterogeneity: Not ap	oplicable							
Test for overall effect:	Z = 0.36 (P =	= 0.72)					Control Very Heavy PAE	

Risk of bias legend

(A) Overall RoB

Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

# **Diagnosed Studies**

# HEART PROBLEMS

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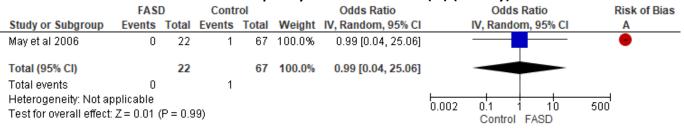
					Hear	t Defect (%)			
		FAS	D and	Freq	uency	of Heart Defect (	%) (1 study)		
	FASD		Contr	ol	-	Odds Ratio	Odd	s Ratio	<b>Risk of Bias</b>
					Weight	IV, Random, 95% CI	IV, Rand	om, 95% Cl	<u>A</u>
May et al 2006	0	22	0	67		Not estimable			-
Total (95% CI)		22		67		Not estimable			
Total events	0		0						
Heterogeneity: Not appli	icable						0.001 0.1	1 10 1	000
Test for overall effect: No	ot applic:	able						I FASD	000
Dick of bice legand									
Risk of bias legend (A) Overall RoB									
(1)									
		FAS	and F	requ	ency of	f Heart Defect (%	(4 studies)		
01 J	FAS		Contr			Odds Ratio		Is Ratio	Risk of Bias
Study or Subgroup Chambers et al 2019	Events 1	lotal 5	Events 1	761		IV, Random, 95% C	,	dom, 95% Cl	
May et al 2007	1	55	0	145	25.7% 24.5%	190.00 [10.04, 3596.91 8.01 [0.32, 199.60			
Mayetal 2013a	O	68	3	90	25.5%	0.18 [0.01, 3.59		<u> </u>	ě
May et al 2020c	0	11	1	521	24.3%	15.09 [0.58, 390.46			- 😑
Total (95% CI)		139		1517	100.0%	8.03 [0.43, 150.80			
Total events	2	100	5	1011	100.070	0.00 [0.40, 100.00			
Heterogeneity: Tau <sup>2</sup> = 6.	46; Chi <b></b> ≇ =	= 10.79,	df = 3 (P	= 0.01	); <b>Iz</b> = 729	6	0.001 0.1		000
Test for overall effect: Z =	= 1.39 (P	= 0.16)						ol FAS	000
Risk of bias legend (A) Overall RoB									
		ρEΛ	Sand	Froqu	oncur	of Haart Dafact (%	) (1 studios)		
	pFA	-		-	ency c	of Heart Defect (%	••••••	s Ratio	Risk of Bias
Study or Subgroup	pFA Events	S	Cont	trol	-	of Heart Defect (% Odds Ratio t IV, Random, 95% CI	Odd	s Ratio om, 95% Cl	Risk of Bias A
Study or Subgroup Chambers et al 2019		S Total	Cont Events	trol Tota	l Weigh	Odds Ratio t IV, Random, 95% CI	Odd		
Chambers et al 2019 May et al 2007	Events 0 1	<b>Total</b> 44 18	Cont Events 1 0	trol Tota 761	Weigh 23.89 23.69	Odds Ratio t IV, Random, 95% CI 5.70 [0.23, 141.84] 5 24.94 [0.98, 636.12]	Odd		
Chambers et al 2019 May et al 2007 May et al 2013a	Events 0 1 0	5 Total 44 18 52	Cont Events 1 0 3	trol Tota 761 145	Veigh 23.89 23.69 25.69	Odds Ratio           t         IV, Random, 95% CI           5.70 [0.23, 141.84]         24.94 [0.98, 636.12]           6         0.24 [0.01, 4.70]	Odd		
Chambers et al 2019 May et al 2007	Events 0 1	5 Total 44 18 52	Cont Events 1 0 3	trol Tota 761 145	Veigh 23.89 23.69 25.69	Odds Ratio t IV, Random, 95% CI 5.70 [0.23, 141.84] 5 24.94 [0.98, 636.12]	Odd		
Chambers et al 2019 May et al 2007 May et al 2013a	Events 0 1 0	5 Total 44 18 52	Cont Events 1 0 3 1	trol 761 761 145 90 521	Veigh 23.89 23.69 25.69	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]	Odd		
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events	Events 0 1 0 1 2	5 Total 44 18 52 23 137	Cont Events 1 0 3 1 5	trol 761 761 145 90 521 1517	<ul> <li>Weigh</li> <li>23.89</li> <li>23.69</li> <li>25.69</li> <li>27.19</li> <li>100.09</li> </ul>	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]           5.26 [0.59, 46.67]	Odd		
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2	Events 0 1 0 1 2 2 :.53; Chi <sup>2</sup>	<b>Total</b> 44 18 52 23 137 = 6.13,	Cont Events 1 0 3 1 1 5 df = 3 (F	trol 761 761 145 90 521 1517	<ul> <li>Weigh</li> <li>23.89</li> <li>23.69</li> <li>25.69</li> <li>27.19</li> <li>100.09</li> </ul>	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]           5.26 [0.59, 46.67]	Odd IV, Rand	om, 95% Cl	
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events	Events 0 1 0 1 2 2 :.53; Chi <sup>2</sup>	<b>Total</b> 44 18 52 23 137 = 6.13,	Cont Events 1 0 3 1 1 5 df = 3 (F	trol 761 761 145 90 521 1517	<ul> <li>Weigh</li> <li>23.89</li> <li>23.69</li> <li>25.69</li> <li>27.19</li> <li>100.09</li> </ul>	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]           5.26 [0.59, 46.67]	Odd IV, Rand	om, 95% CI	A •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2	Events 0 1 0 1 2 2 :.53; Chi <sup>2</sup>	<b>Total</b> 44 18 52 23 137 = 6.13,	Cont Events 1 0 3 1 1 5 df = 3 (F	trol 761 761 145 90 521 1517	<ul> <li>Weigh</li> <li>23.89</li> <li>23.69</li> <li>25.69</li> <li>27.19</li> <li>100.09</li> </ul>	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]           5.26 [0.59, 46.67]	Odd IV, Rand	om, 95% Cl	A •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z	Events 0 1 0 1 2 2 :.53; Chi <sup>2</sup>	<b>Total</b> 44 18 52 23 137 = 6.13,	Cont Events 1 0 3 1 1 5 df = 3 (F	trol 761 761 145 90 521 1517	<ul> <li>Weigh</li> <li>23.89</li> <li>23.69</li> <li>25.69</li> <li>27.19</li> <li>100.09</li> </ul>	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]           5.26 [0.59, 46.67]	Odd IV, Rand	om, 95% Cl	A •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u>	Events 0 1 0 1 2 2 :.53; Chi <sup>2</sup>	<b>Total</b> 44 18 52 23 137 = 6.13,	Cont Events 1 0 3 1 1 5 df = 3 (F	trol 761 761 145 90 521 1517	<ul> <li>Weigh</li> <li>23.89</li> <li>23.69</li> <li>25.69</li> <li>27.19</li> <li>100.09</li> </ul>	Odds Ratio           IV, Random, 95% CI           5.70 [0.23, 141.84]           24.94 [0.98, 636.12]           0.24 [0.01, 4.70]           23.64 [1.43, 390.42]           5.26 [0.59, 46.67]	Odd IV, Rand	om, 95% Cl	A •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u>	Events 0 1 0 1 2 .53; Chi <sup>a</sup> = 1.49 (F	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14	Coni <u>Events</u> 3 1 5 df = 3 (F )	trol 761 145 90 521 <b>1517</b> ? = 0.11	Weigh           23.89           23.69           25.69           27.19           100.09           ); I <sup>2</sup> = 51 <sup>+</sup>	Odds Ratio  t IV, Random, 95% CI  5.70 [0.23, 141.84]  24.94 [0.98, 636.12]  0.24 [0.01, 4.70]  23.64 [1.43, 390.42]  5.26 [0.59, 46.67]  %	Odd IV, Rand 	om, 95% CI	A •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u>	Events 0 1 0 1 2 .53; Chi <sup>a</sup> = 1.49 (F	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14	Coni <u>Events</u> 1 0 3 1 5 df = 3 (F ) thers a	trol 761 145 90 521 1517 9 = 0.11	Weigh           23.89           23.69           23.69           25.69           27.19           100.09           ); I <sup>2</sup> = 51 <sup>1</sup>	Odds Ratio t IV, Random, 95% CI 5.70 [0.23, 141.84] 24.94 [0.98, 636.12] 0.24 [0.01, 4.70] 23.64 [1.43, 390.42] 5.26 [0.59, 46.67] %	Odd IV, Rand 	om, 95% CI	A 
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u>	Events 0 1 0 1 2 .53; Chi² = 1.49 (F ARI A	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14	Comi <u>Events</u> 1 0 3 1 5 df = 3 (F ) thers a hers	trol Tota 761 145 90 521 1517 - - 0.11 - - 0.11 - - - - - - - - - - - - -	Weigh           23.89           23.69           23.69           25.69           27.19           100.09           ); I* = 51'	Odds Ratio  t IV, Random, 95% CI  5.70 [0.23, 141.84]  24.94 [0.98, 636.12]  0.24 [0.01, 4.70]  23.64 [1.43, 390.42]  5.26 [0.59, 46.67]  %	Odd IV, Rand 	om, 95% CI	A •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR	Events 0 1 0 1 2 .53; Chi <sup>2</sup> = 1.49 (F ARI A E	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14	Comi <u>Events</u> 1 0 3 1 5 df = 3 (F ) thers a hers	trol Tota 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11 1 = 0.11 2 = 0.11	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51'           requeint           rol           Total V           761	Odds Ratio  t IV, Random, 95% CI  5.70 [0.23, 141.84] 24.94 [0.98, 636.12] 23.64 [1.43, 390.42] 23.64 [1.43, 390.42] 5.26 [0.59, 46.67] %  http://dx.actionum.com/distribution/distributicom/distributicom/distributicom/distributicom/distributicom/distrib	Odd IV, Rand 	om, 95% CI	A 
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR May et al 2013a (ARND)	Events 0 1 0 1 2 .53; Chi <sup>2</sup> = 1.49 (F ARI A E	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14 ND/O RND/Ot vents 0 0	Com <u>Events</u> 1 0 3 1 5 df = 3 (F ) thers a hers <u>Total F</u> 44 35	trol Tota 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11 3	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51 <sup>+</sup> requeint           ol           Total V           761           90	Odds Ratio  t IV, Random, 95% CI  5.70 [0.23, 141.84] 24.94 [0.98, 636.12] 23.64 [1.43, 390.42] 23.64 [1.43, 390.42] 5.26 [0.59, 46.67]  %  http://doi.org/10.23, 141.35.6% 5.70 [0.23, 141.35.6% 0.35 [0.02, 6]	Odd IV, Rand 	om, 95% CI	A 
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR	Events 0 1 0 1 2 .53; Chi <sup>2</sup> = 1.49 (F ARI A E	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14 <b>ND/O</b> <b>RND/Ot</b> vents 0	Coni <u>Events</u> 1 0 3 1 5 df = 3 (F ) thers a hers <u>Total B</u> 44	trol Tota 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11 1 = 0.11 2 = 0.11	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51 <sup>+</sup> requeint           ol           Total V           761           90	Odds Ratio  t IV, Random, 95% CI  5.70 [0.23, 141.84] 24.94 [0.98, 636.12] 23.64 [1.43, 390.42] 23.64 [1.43, 390.42] 5.26 [0.59, 46.67] %  http://dx.actionum.com/distribution/distributicom/distributicom/distributicom/distributicom/distributicom/distrib	Odd IV, Rand 	om, 95% CI	A 
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR May et al 2013a (ARND) May et al 2020c (ARND)	Events 0 1 0 1 2 .53; Chi <sup>2</sup> = 1.49 (F ARI A E	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14 <b>ND/O</b> <b>RND/O</b> <b>RND/O</b> 0 0 0	Com <u>Events</u> 1 0 3 1 5 df = 3 (F ) thers a hers <u>Total F</u> 44 35	trol Tota 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 3 1 3 1	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51 <sup>+</sup> requeint           ol           Total V           761           90	Odds Ratio  t IV, Random, 95% CI  5 .70 [0.23, 141.84] 24.94 [0.98, 636.12] 0 .24 [0.01, 4.70] 23.64 [1.43, 390.42] 5 .26 [0.59, 46.67]  5.26 [0.59, 46.67]   where the second state of th	Odd IV, Rand 0.001 0.1 Contro Ct (%) (3 stud O CI IV, Ra 341 391	om, 95% CI	A 
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR May et al 2013a (ARND) May et al 2020c (ARND) <b>Total (95% CI)</b> Total events	Events 0 1 0 1 2 .53; Chi <sup>a</sup> = 1.49 (F ARI A E <sup>i</sup> ND)	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, P = 0.14 <b>ND/O</b> <b>RND/Ot</b> <b>Vents</b> 0 0 0	Com Events 1 0 3 1 5 df = 3 (F ) thers a hers Total I 44 35 10 89	trol 761 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51''           requein           rol           Total V           90           521           1372	Odds Ratio  t IV, Random, 95% CI  5 .70 [0.23, 141.84] 24.94 [0.98, 636.12] 0 .24 [0.01, 4.70] 23.64 [1.43, 390.42] 5 .26 [0.59, 46.67]  5.26 [0.59, 46.67]   w  http://doi.org/10.023/141 0.045 Ratio Veight IV, Random, 959 0.25% 5.70 [0.23, 141 0.35.6% 0.35 [0.02, 6 0.31.9% 16.52 [0.64, 429]	Odd IV, Rand 0.001 0.1 Contro Ct (%) (3 stud O CI IV, Ra 341 391	om, 95% CI	A 
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR May et al 2013a (ARND) May et al 2020c (ARND) <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 1.52	Events 0 1 0 1 2 .53; Chi <sup>a</sup> = 1.49 (F ARI A E <sup>i</sup> ND)	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, = 0.14 <b>ND/O</b> <b>RND/Ot</b> <b>Vents</b> 0 0 0 3.18, df:	Com Events 1 0 3 1 5 df = 3 (F ) thers a hers Total I 44 35 10 89	trol 761 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51''           requein           rol           Total V           90           521           1372	Odds Ratio  t IV, Random, 95% CI  5 .70 [0.23, 141.84] 24.94 [0.98, 636.12] 0 .24 [0.01, 4.70] 23.64 [1.43, 390.42] 5 .26 [0.59, 46.67]  5.26 [0.59, 46.67]   w  http://doi.org/10.023/141 0.045 Ratio Veight IV, Random, 959 0.25% 5.70 [0.23, 141 0.35.6% 0.35 [0.02, 6 0.31.9% 16.52 [0.64, 429]	Odd IV, Rand 	om, 95% CI	A - • • • • • • • • • • • • • • • • • • •
Chambers et al 2019 May et al 2007 May et al 2013a May et al 2020c <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z <u>Risk of bias legend</u> (A) Overall RoB <u>Study or Subgroup</u> Chambers et al 2019 (AR May et al 2013a (ARND) May et al 2020c (ARND) <b>Total (95% CI)</b> Total events	Events 0 1 0 1 2 .53; Chi <sup>a</sup> = 1.49 (F ARI A E <sup>i</sup> ND)	<b>Total</b> 44 18 52 23 <b>137</b> = 6.13, = 0.14 <b>ND/O</b> <b>RND/Ot</b> <b>Vents</b> 0 0 0 3.18, df:	Com Events 1 0 3 1 5 df = 3 (F ) thers a hers Total I 44 35 10 89	trol 761 761 145 90 521 1517 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11 2 = 0.11	Weigh           23.89           23.69           25.69           27.19           100.09           7           100.09           ); I <sup>2</sup> = 51''           requein           rol           Total V           90           521           1372	Odds Ratio  t IV, Random, 95% CI  5 .70 [0.23, 141.84] 24.94 [0.98, 636.12] 0 .24 [0.01, 4.70] 23.64 [1.43, 390.42] 5 .26 [0.59, 46.67]  5.26 [0.59, 46.67]   w  http://doi.org/10.023/141 0.045 Ratio Veight IV, Random, 959 0.25% 5.70 [0.23, 141 0.35.6% 0.35 [0.02, 6 0.31.9% 16.52 [0.64, 429]	Odd IV, Rand 	ies) dds Ratio indom, 95% Cl	A - • • • • • • • • • • • • • • • • • • •

Risk of bias legend (A) Overall RoB

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Notes: All papers used some form of the IOM diagnostic criteria. May et al 2013a also reports non-syndromal.

### FASD and Frequency of Heart Murmur (%) (1 study)



#### Risk of bias legend

(A) Overall RoB

# FAS and Frequency of Heart Murmur (%) (5 studies)

	FAS		Contr	lo	-	Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Chambers et al 2019	1	5	14	761	10.7%	13.34 [1.40, 127.09]	
May et al 2007	6	55	5	145	31.9%	3.43 [1.00, 11.74]	
May et al 2013a	12	68	6	90	42.3%	3.00 [1.06, 8.46]	⊢∎- ●
May et al 2015	1	7	2	190	8.5%	15.67 [1.24, 197.53]	
Viljoen et al 2005	6	64	0	146	6.6%	32.56 [1.81, 587.17]	│ ——— ●
Total (95% CI)		199		1332	100.0%	4.95 [2.32, 10.53]	◆
Total events	26		27				
Heterogeneity: Tau² = 0	.07; Chi <b>²</b> =	= 4.38,	df = 4 (P	= 0.36)	; I² = 9%		
Test for overall effect: Z	= 4.15 (P	< 0.00	01)				0.002 0.1 1 10 500 Control FAS

#### Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Heart Murmur (%) (5 studies)

	pFA	S	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	1	39	2	179	8.7%	2.33 [0.21, 26.35]			?
Chambers et al 2019	2	44	14	761	22.2%	2.54 [0.56, 11.55]		+	•
May et al 2007	4	18	5	145	25.1%	8.00 [1.92, 33.26]			•
May et al 2013a	7	52	6	90	38.6%	2.18 [0.69, 6.87]		+	•
May et al 2015	0	19	2	190	5.4%	1.93 [0.09, 41.73]			•
Total (95% CI)		172		1365	100.0%	3.12 [1.53, 6.38]		◆	
Total events	14		29						
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.27, df =	4 (P = 0.6)	69); I <sup>z</sup> =	0%				0.002		500
Test for overall effect: Z = 3.13 (P = 0.002)							0.002	Control pFAS	500

# Risk of bias legend

(A) Overall RoB

# ARND/Others and Frequency of Heart Murmur (%) (2 studies)

	ARND/Ot	hers	Cont	lo		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
Chambers et al 2019 (ARND)	1	44	14	761	33.1%	1.24 [0.16, 9.66]			•
May et al 2013a (ARND)	3	35	6	90	66.9%	1.31 [0.31, 5.56]			•
Total (95% CI)		79		851	100.0%	1.29 [0.40, 4.20]		•	
Total events	4		20						
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi Test for overall effect: Z = 0.42 (		= 1 (P =	: 0.97); I²	= 0%			0.002	0.1 1 10 Control ARND/Othe	500 rs

Risk of bias legend

(A) Overall RoB

Notes: All papers used some form of the IOM diagnostic criteria. May et al 2013a also reports non-syndromal.

#### Hypertrichosis (%) FASD and Frequency of Hypertrichosis (%) (1 study) FASD Control Odds Ratio Odds Ratio Risk of Bias Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup Α May et al 2006 0 22 0 67 Not estimable Total (95% CI) 22 67 Not estimable 0 0 Total events Heterogeneity: Not applicable 0.005 0.1 200 10 Test for overall effect: Not applicable Control FASD Risk of bias legend (A) Overall RoB FAS and Frequency of Hypertrichosis (%) (3 studies) FAS Control Odds Ratio **Risk of Bias** Odds Ratio Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI A May et al 2007 0 55 0 145 Not estimable May et al 2015 1 7 3 190 50.3% 10.39 [0.94, 115.06] Viljoen et al 2005 2 64 49.7% 4.68 [0.42, 52.54] 1 146 Total (95% CI) 481 100.0% 6.99 [1.27, 38.45] 126 Total events 3 4 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.21, df = 1 (P = 0.65); l<sup>2</sup> = 0% 0.005 0'1 200 10 Test for overall effect: Z = 2.23 (P = 0.03) Control FAS Risk of bias legend (A) Overall RoB pFAS and Frequency of Hypertrichosis (%) (1 study) pFAS Control Odds Ratio Odds Ratio Risk of Bias IV, Random, 95% CI Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Α May et al 2007 18 n 145 100.0% 24.94 [0.98, 636.12] 1 Total (95% CI) 145 100.0% 24.94 [0.98, 636.12] 18 Total events 0 1

Heterogeneity: Not applicable Test for overall effect: Z = 1.95 (P = 0.05)

Risk of bias legend (A) Overall RoB

Notes: All papers used some form of the IOM diagnostic criteria.

# HYPOPLASTIC NAILS

#### Hypoplastic Nails (%) FASD and Frequency of Hypoplastic Nails (%) (1 study) FASD Control Odds Ratio Odds Ratio Risk of Bias Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI Δ May et al 2006 22 0 67 Not estimable 0 Total (95% CI) 22 67 Not estimable Total events 0 0 Heterogeneity: Not applicable 0.001 0.1 10 1000 Test for overall effect: Not applicable Control FASD Risk of bias legend

0.001

0.1

1

pFAS Control

1000

10

(A) Overall RoB

# FAS and Frequency of Hypoplastic Nails (%) (4 studies)

	FAS	5	Cont	rol		Odds Ratio		Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	Α
May et al 2007	6	55	2	145	46.1%	8.76 [1.71, 44.81]			•
May et al 2013a	4	68	2	90	41.2%	2.75 [0.49, 15.48]			•
May et al 2020a	0	4	0	278		Not estimable			•
May et al 2020b	0	8	2	413	12.7%	9.68 [0.43, 217.39]			- •
Total (95% CI)		135		926	100.0%	5.50 [1.82, 16.68]		•	
Total events	10		6						
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	•		•	(P = 0.5	9); I² = 09	6	0.001	0.1 1 10	1000
restion overall effect.	2 - 0.01	() = 0.c	,00,					Control FAS	

### Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Hypoplastic Nails (%) (4 studies)

	pFA	S	Cont	rol		Odds Ratio	Odds Ratio Ri	sk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	Α
May et al 2007	0	18	2	145	15.8%	1.55 [0.07, 33.58]		
May et al 2013a	3	52	2	90	45.0%	2.69 [0.44, 16.68]		
May et al 2020a	1	22	0	278	14.3%	38.86 [1.54, 982.90]	(	
May et al 2020b	1	16	2	413	24.8%	13.70 [1.18, 159.58]		
Total (95% CI)		108		926	100.0%	5.42 [1.59, 18.41]	◆	
Total events	5		6					
Heterogeneity: Chi <sup>2</sup> =	3.18, df=	3 (P =	0.37); l² =	= 6%				
Test for overall effect:	Z= 2.71	(P = 0.0	007)				0.001 0.1 1 10 1000 Control pFAS	

#### Risk of bias legend

(A) Overall RoB

# ARND/Others and Frequency of Hypoplastic Nails (%) (3 studies)

	ARND/Ot	hers	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013a (ARND)	2	35	2	90	70.1%	2.67 [0.36, 19.71]		•
May et al 2020a (ARND)	0	12	0	278		Not estimable		•
May et al 2020b (ARND)	0	25	2	413	29.9%	3.23 [0.15, 69.01]		•
Total (95% CI)		72		781	100.0%	2.82 [0.53, 15.07]	-	
Total events	2		4					
Heterogeneity: Tau <sup>2</sup> = 0.00	l; Chi² = 0.0	01, df=	1 (P = 0.9	92); I <sup>2</sup> =	0%			
Test for overall effect: Z = 1	.21 (P = 0.	22)					0.001 0.1 1 10 10 Control ARND/Others	100

Risk of bias legend (A) Overall RoB

Notes: All papers used some form of the IOM diagnostic criteria. May et al 2013a also reports non-syndromal.

#### CAMPTODACTYLY

#### Camptodactyly (%) FASD and Frequency of Camptodactyly (1 study) Odds Ratio FASD Control Odds Ratio Risk of Bias Events Total Events Total Weight IV, Random, 95% CI Study or Subgroup IV, Random, 95% CI Δ May et al 2006 22 5 67 100.0% 3.65 [0.94, 14.08] 5 Total (95% CI) 22 67 100.0% 3.65 [0.94, 14.08] Total events 5 5 Heterogeneity: Not applicable 0.01 0.1 100 1 10 Test for overall effect: Z = 1.88 (P = 0.06) Control FASD

# FAS and Frequency of Camptodactyly (6 studies)

	FAS		Contr	ol	-	Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total I	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
May et al 2007	20	55	12	145	31.0%	6.33 [2.83, 14.19]	•
May et al 2013a	19	68	6	90	20.9%	5.43 [2.03, 14.51]	<b>_--</b> ●
May et al 2015	2	19	11	190	8.0%	1.91 [0.39, 9.36]	•
May et al 2017	29	129	6	104	23.8%	4.74 [1.88, 11.91]	→→ ●
May et al 2020c	2	11	12	521	7.6%	9.43 [1.84, 48.38]	— • • •
Viljoen et al 2005	13	64	2	146	8.7%	18.35 [4.00, 84.13]	│ <del>─</del> ●
Total (95% CI)		346		1196	100.0%	5.88 [3.75, 9.21]	•
Total events	85		49				
Heterogeneity: Tau² =	: 0.00; Chi <sup>z</sup>	= 4.66,	df = 5 (	P = 0.4	6); I <b>²</b> = 0%	6	
Test for overall effect:	Z=7.72 (F	P < 0.00	0001)				0.01 0.1 1 10 100 Control FAS

# Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Camptodactyly (6 studies)

	pFA	s	Contr	rol		Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl A
May et al 2010 - Italian Cohort (FAS/pFAS)	5	39	15	179	22.0%	1.61 [0.55, 4.72]	?
May et al 2007	5	18	12	145	20.1%	4.26 [1.30, 13.99]	<b>→</b> ●
May et al 2013a	12	52	6	90	22.5%	4.20 [1.47, 12.00]	<b>_--</b> ●
May et al 2015	2	7	11	190	12.7%	6.51 [1.13, 37.43]	●
May et al 2017	3	100	6	104	16.7%	0.51 [0.12, 2.08]	
May et al 2020c	0	23	12	521	6.0%	0.87 [0.05, 15.09]	
Total (95% CI)		239		1229	100.0%	2.31 [1.08, 4.92]	◆
Total events	27		62				
Heterogeneity: Tau <sup>2</sup> = 0.38; Chi <sup>2</sup> = 8.92, df =	5 (P = 0.1	1); I <sup>z</sup> =	44%				
Test for overall effect: Z = 2.16 (P = 0.03)							0.01 0.1 1 10 100 Control pFAS

#### Risk of bias legend (A) Overall RoB

# ARND/Others and Frequency of Camptodactyly (3 studies)

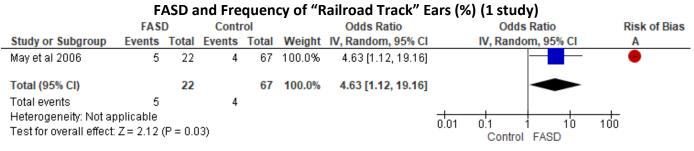
	ARND/Of	thers	Cont	rol	-	Odds Ratio	Odds Ratio Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl A
May et al 2013a (ARND)	4	35	6	90	44.3%	1.81 [0.48, 6.83]	
May et al 2017 (ARND)	3	55	6	104	38.6%	0.94 [0.23, 3.92]	<b>+</b> •
May et al 2020c (ARND)	1	10	12	521	17.1%	4.71 [0.55, 40.21]	<b>→</b> • •
Total (95% CI)		100		715	100.0%	1.66 [0.68, 4.01]	•
Total events	8		24				
Heterogeneity: Tau <sup>2</sup> = 0.0	0; Chi <sup>2</sup> = 1.	53, df=	2 (P = 0.4	47); I <sup>z</sup> =	0%		
Test for overall effect: Z =	1.12 (P = 0	.26)					0.01 0.1 1 10 100 Control ARND/Others
Dist. Altist Issued							

Risk of bias legend (A) Overall RoB

*Notes:* All papers used some form of the IOM diagnostic criteria except Viljoen et al 2005 (Walldrop's checklist). May et al 2013 a also reported non-syndromal.

# "RAILROAD TRACK" EARS

# "Railroad Track" Ears (%)



# FAS and Frequency of "Railroad Track" Ears (%) (4 studies)

	FAS	;	Contr	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	8	55	4	145	22.0%	6.00 [1.73, 20.83]		•
May et al 2013a	7	68	5	90	23.4%	1.95 [0.59, 6.44]	+ <b>-</b>	•
May et al 2017	69	129	14	104	45.7%	7.39 [3.82, 14.32]		•
Viljoen et al 2005	5	64	1	164	8.9%	13.81 [1.58, 120.69]		- •
Total (95% CI)		316		503	100.0%	5.47 [2.75, 10.87]	•	
Total events	89		24					
Heterogeneity: Tau <sup>2</sup> =	= 0.16; Chi	i <sup>z</sup> = 4.3	4, df = 3 (	P = 0.2	3); I <sup>z</sup> = 31	%		+
Test for overall effect	Z = 4.85	(P < 0.0	00001)				0.01 0.1 1 10 Control FAS	100

#### Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of "Railroad Track" Ears (%) (4 studies)

•						• • •	· · · ·	
	pFA	S	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	5	39	12	179	25.0%	2.05 [0.68, 6.19]		?
May et al 2007	3	18	4	145	13.1%	7.05 [1.44, 34.53]	— <b>-</b> —	•
May et al 2013a	3	52	5	90	15.1%	1.04 [0.24, 4.54]	<b>_</b>	•
May et al 2017	20	100	14	104	46.8%	1.61 [0.76, 3.39]	+=-	•
Total (95% CI)		209		518	100.0%	1.94 [1.07, 3.53]	◆	
Total events	31		35					
Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 3.47, df =	3 (P = 0.0	33); I <sup>z</sup> =	13%				0.01 0.1 1 10 100	
Test for overall effect: Z = 2.17 (P = 0.03)							0.01 0.1 1 10 100 Control pFAS	

#### Risk of bias legend (A) Overall RoB

# ARND/Others and Frequency of "Railroad Track" Ears (%) (2 studies)

	ARND/Ot	hers	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013a (ARND)	2	35	5	90	24.9%	1.03 [0.19, 5.57]		•
May et al 2017 (ARND)	7	55	14	104	75.1%	0.94 [0.35, 2.48]		•
Total (95% CI)		90		194	100.0%	0.96 [0.41, 2.23]	•	
Total events	9		19					
Heterogeneity: Tau <sup>2</sup> = 0.0	0; Chi² = 0.0	01, df=	1 (P = 0.9	32); I <b>2</b> =	0%			<del>1.</del>
Test for overall effect: Z =	0.10 (P = 0	.92)					0.01 0.1 1 10 1 Control ARND/Others	00
Risk of bias legend								

(A) Overall RoB

Notes: All papers used some form of the IOM diagnostic criteria. May et al 2013a also reports non-syndromal.

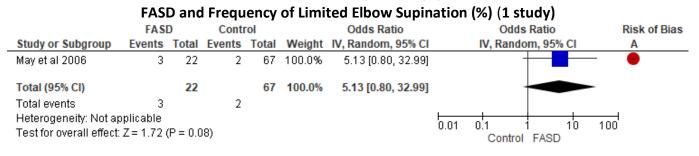
# OTHER EAR ABNORMALITIES

# Other Ear Abnormalities - Low-Set Ears (%) FASD and Frequency of Low Set Fars (%) (1 study)

		B and		ieney e			
FAS	D	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bias
Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Α
2	93	15	761	57.0%	1.09 [0.25, 4.86]		•
7	26	1	27	43.0%	9.58 [1.09, 84.50]		- •
	119		788	100.0%	2.78 [0.34, 22.87]		
9		16					
.45; Chi <b>²</b> :	= 2.60,	df = 1 (P	= 0.11)	; <b>I<sup>2</sup> =</b> 62%			<del></del>
= 0.95 (P	= 0.34)	)				Control FASD	00
	Events 2 7 9 .45; Chi <sup>2</sup>	FASD           Events         Total           2         93           7         26           119         9           .45; Chi² = 2.60,	FASD         Contr           Events         Total         Events           2         93         15           7         26         1           119           9         16	FASD         Control           Events         Total         Events         Total           2         93         15         761           7         26         1         27           119         788           9         16           45; Chi² = 2.60, df = 1 (P = 0.11)         10	FASD         Control           Events         Total         Events         Total         Weight           2         93         15         761         57.0%           7         26         1         27         43.0%           9         16         788         100.0%           9         16         45; Chi² = 2.60, df = 1 (P = 0.11); l² = 62%	FASD         Control         Odds Ratio           Events         Total         Events         Total         Weight         IV, Random, 95% CI           2         93         15         761         57.0%         1.09 [0.25, 4.86]           7         26         1         27         43.0%         9.58 [1.09, 84.50]           119         788         100.0%         2.78 [0.34, 22.87]           9         16         .45; Chi² = 2.60, df = 1 (P = 0.11); I² = 62%         .45	Events         Total         Events         Total         Weight         IV, Random, 95% Cl         IV, Random, 95% Cl           2         93         15         761         57.0%         1.09 [0.25, 4.86]

### **DECREASED JOINT SUPINATION**

### Limited Elbow Supination (%)



Risk of bias legend

(A) Overall RoB

# FAS and Frequency of Limited Elbow Supination (%) (4 studies)

	FAS		Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019	1	5	21	761	24.0%	8.81 [0.94, 82.24]		- 🗕
May et al 2007	2	55	1	145	20.4%	5.43 [0.48, 61.17]		- 😑
May et al 2013a	1	68	1	90	15.4%	1.33 [0.08, 21.62]		•
Viljoen et al 2005	4	64	2	146	40.3%	4.80 [0.86, 26.91]	<b>⊢</b> ∎	•
Total (95% CI)		192		1142	100.0%	4.67 [1.57, 13.95]	•	
Total events	8		25					
Heterogeneity: Tau <sup>2</sup> = 0	).00; Chi <b>²</b> =	= 1.11,	df = 3 (P	= 0.78)	; I <sup>z</sup> = 0%			<del></del>
Test for overall effect: Z	= 2.76 (P	= 0.00	6)				0.01 0.1 1 10 1 Control FAS	00

Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Limited Elbow Supination (%) (3 studies)

	pFA	S	Cont	rol		Odds Ratio	Odds Ratio	<b>Risk of Bias</b>
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019	4	44	21	761	73.2%	3.52 [1.15, 10.75]	<b>∎</b>	•
May et al 2007	2	18	1	145	15.1%	18.00 [1.54, 209.72]	<b>-</b>	→ 😑
May et al 2013a	1	52	1	90	11.7%	1.75 [0.11, 28.50]		•
Total (95% CI)		114		996	100.0%	4.15 [1.60, 10.79]	•	
Total events	7		23					
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	•	•	4	= 0.40)	; I² = 0%			100
restior overall ellect. Z	– 2.82 (F	- 0.00	3)				Control pFAS	

Risk of bias legend

(A) Overall RoB

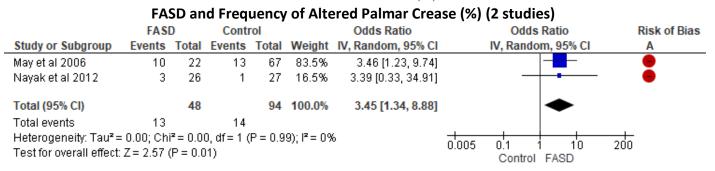
ARND/Others and Frequency of Limited Elbow Supination (%) (2 studies)

	ARND/Ot	hers	Cont	rol		Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
Chambers et al 2019 (ARND)	0	44	21	761	56.7%	0.39 [0.02, 6.49]	
May et al 2013a (ARND)	0	35	1	90	43.3%	0.84 [0.03, 21.12]	
Total (95% CI)		79		851	100.0%	0.54 [0.06, 4.52]	
Total events	0		22				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>3</sup>	<sup>2</sup> = 0.13, df :	= 1 (P =	: 0.72); I <sup>2</sup>	= 0%			
Test for overall effect: $Z = 0.57$ (	P = 0.57)						Control ARND/Others

Risk of bias legend (A) Overall RoB

Notes: All papers used some form of the IOM diagnostic criteria. May et al 2013a also reports non-syndromal.

### Altered Palmar Crease (%)



#### Risk of bias legend (A) Overall RoB

### FAS and Frequency of Altered Palmar Crease (%) (6 studies)

	FAS		Contr	ol		Odds Ratio	Odds Ratio Risk of Bia
Study or Subgroup	Ibgroup Events Total Events Total Weight IV, Random, 9		IV, Random, 95% CI	IV, Random, 95% CI A			
Chambers et al 2019	2	5	15	761	4.6%	33.16 [5.16, 213.15]	
May et al 2007	24	55	38	145	22.7%	2.18 [1.14, 4.17]	│
May et al 2013a	33	68	19	90	21.0%	3.52 [1.76, 7.06]	🗕 😑
May et al 2017	59	129	24	104	25.8%	2.81 [1.58, 4.98]	🗕 😑
May et al 2020c	1	11	11	521	3.6%	4.64 [0.55, 39.43]	
Viljoen et al 2005	26	64	25	146	22.3%	3.31 [1.71, 6.40]	· · •
Total (95% CI)		332		1767	100.0%	3.29 [2.16, 5.00]	. ♦
Total events	145		132				
Heterogeneity: Tau <sup>2</sup> = 0	).09; Chi <b>²</b> =	= 7.78,	df = 5 (P	= 0.17)	; I <b>²</b> = 36%	I. Contraction of the second se	
Test for overall effect: Z	:= 5.58 (P	< 0.00	001)				0.001 0.1 1 10 1000 Control FAS

#### Risk of bias legend

(A) Overall RoB

# pFAS and Frequency of Altered Palmar Crease (%) (6 studies)

	pFA	s	Contr	ol		Odds Ratio	Odds Ratio Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI A
May et al 2010 - Italian Cohort (FAS/pFAS)	14	39	41	179	22.1%	1.88 [0.90, 3.96]	?
Chambers et al 2019	1	44	15	761	4.7%	1.16 [0.15, 8.96]	
May et al 2007	7	18	38	145	14.8%	1.79 [0.65, 4.96]	_ <b>↓</b> •─ ●
May et al 2013a	15	52	19	90	20.7%	1.51 [0.69, 3.32]	+•- •
May et al 2017	32	100	24	104	26.5%	1.57 [0.84, 2.92]	+ 🖢
May et al 2020c	4	23	11	521	11.2%	9.76 [2.85, 33.48]	
Total (95% CI)		276		1800	100.0%	2.00 [1.25, 3.19]	◆
Total events	73		148				
Heterogeneity: Tau <sup>2</sup> = 0.11; Chi <sup>2</sup> = 7.70, df =	5 (P = 0.1	7); I² =	35%				
Test for overall effect: Z = 2.90 (P = 0.004)							Control pFAS

#### Risk of bias legend (A) Overall RoB

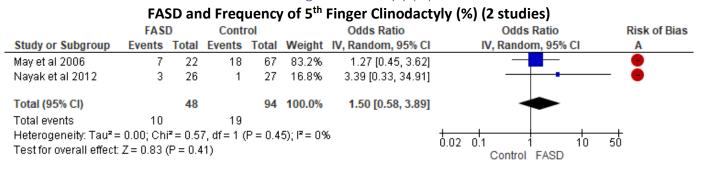
# ARND/Others and Frequency of Altered Palmar Crease (%) (4 studies)

	/ • • • • • •				0.7.00			
	ARND/Ot	thers	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Chambers et al 2019 (ARND)	1	44	14	761	6.6%	1.24 [0.16, 9.66]		•
May et al 2013a (ARND)	13	35	19	90	38.1%	2.21 [0.94, 5.18]	-∎-	•
May et al 2017 (ARND)	15	55	24	104	49.4%	1.25 [0.59, 2.64]		•
May et al 2020c (ARND)	1	10	11	521	6.0%	5.15 [0.60, 44.25]	+	•
Total (95% CI)		144		1476	100.0%	1.69 [1.00, 2.86]	•	
Total events	30		68					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	<sup>2</sup> = 2.12, df	= 3 (P =	: 0.55); I <sup>z</sup>	= 0%				<del></del>
Test for overall effect: Z = 1.95 (I		Ì					0.005 0.1 1 10 2 Control ARND/Others	00

#### Risk of bias legend (A) Overall RoB

*Notes:* All papers used some form of the IOM diagnostic criteria except Nayak et al 2012 (Walldrop's checklist). Chambers et al 2019 reports both single transverse palmar crease and hypoplastic palmar crease, used former. May et al 2013 also reports non-syndromal.

# 5<sup>th</sup> Finger Clinodactyly (%)



#### Risk of bias legend

(A) Overall RoB

# FAS and Frequency of 5<sup>th</sup> Finger Clinodactyly (%) (5 studies)

						0		
	FAS	5	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2007	28	55	64	145	31.4%	1.31 [0.70, 2.44]	- <b>-</b>	•
May et al 2013a	41	68	59	90	28.6%	0.80 [0.42, 1.53]		•
May et al 2014	5	12	46	162	8.5%	1.80 [0.54, 5.96]		•
May et al 2015	1	7	55	190	2.7%	0.41 [0.05, 3.48]		•
Viljoen et al 2005	20	64	36	146	28.9%	1.39 [0.73, 2.66]		•
Total (95% CI)		206		733	100.0%	1.15 [0.81, 1.63]	•	
Total events	95		260					
Heterogeneity: Tau <sup>2</sup> :	= 0.00; Ch	i² = 3.1	4, df = 4 (	(P = 0.5	3); I <sup>z</sup> = 09	6		
Test for overall effect	t: Z = 0.80	(P = 0.4	3)	•			0.02 0.1 1 10 Control FAS	50

Risk of bias legend (A) Overall RoB

# pFAS and Frequency of 5<sup>th</sup> Finger Clinodactyly (%) (5 studies)

	pFA	S	Contr	ol		Odds Ratio	Odds Ratio	Risk of Bia
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2010 - Italian Cohort (FAS/pFAS)	21	39	58	179	24.0%	2.43 [1.20, 4.92]		?
May et al 2007	11	18	64	145	16.4%	1.99 [0.73, 5.42]	+	•
May et al 2013a (ARND)	33	52	59	90	23.7%	0.91 [0.45, 1.86]		•
May et al 2014	14	23	46	162	18.5%	3.92 [1.59, 9.69]		•
May et al 2015	10	19	55	190	17.4%	2.73 [1.05, 7.08]		•
Total (95% CI)		151		766	100.0%	2.08 [1.24, 3.48]	•	
Total events	89		282					
Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 7.50, df =	4 (P = 0.1	1); I <sup>2</sup> =	47%					<del></del>
Test for overall effect: Z = 2.79 (P = 0.005)							0.02 0.1 1 10 Favours Control Favours pFAS	50

Risk of bias legend (A) Overall RoB

# ARND/Others and Frequency of 5<sup>th</sup> Finger Clinodactyly (%) (2 studies)

	ARND/Ot	thers	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
May et al 2013a (ARND)	17	35	59	90	57.2%	0.50 [0.22, 1.10]		•
May et al 2014 (ARND)	5	13	46	162	42.8%	1.58 [0.49, 5.07]		•
Total (95% CI)		48		252	100.0%	0.81 [0.27, 2.50]	-	
Total events	22		105					
Heterogeneity: Tau <sup>2</sup> = 0.4	1; Chi <sup>2</sup> = 2.	57, df=	1 (P = 0.1)	11); I <sup>2</sup> =	61%			50
Test for overall effect: Z =	0.36 (P = 0	.72)					Control ARND/Others	

Risk of bias legend (A) Overall RoB

Notes: All papers used some form of the IOM diagnostic criteria except Viljoen et al 2005 (Walldrop's checklist). May et al 2013 a also reports nonsyndromal.

# Summary of available outcomes for dysmorphology checklist

Outcome	Eexposure/ Diagnosis	Outcome	# Studies
	Exposure studies	Dysmorphology score (m/SD)	<b>2 studies:</b> 1 moderate PAE and 2
Dysmorphology Score			very heavy PAE
	Diagnosed studies	Dysmorphology score (m/SD)	<b>14 studies</b> with 3 FASD, 8 FAS, 8
			pFAS, 4 ARND/Other

# GRADE ratings for dysmorphology checklist

		Cert	tainty assessn	nent		Nº of p	atients	[	Effect	
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% Cl)	Certainty
EXPOSU	RE STUDIE	S								
Dysmorp	phology So	core (m/SD)								
Moderat	e PAE									
1	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	45	253	-	SMD 0.8 higher (0.47 higher to 1.12 higher)	⊕⊕⊖⊖ Low
Very Hea	avy PAE									
2	serious <sup>a</sup>	not serious	not serious	serious <sup>e,f</sup>	none	44	274	-	SMD 1.22 higher (0.75 higher to 1.69 higher)	⊕⊕⊖⊖ Low
DIAGNO	SED STUD	IES								
Dysmorp	hology So	core								
FASD										
3	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e,f</sup>	none	89	183	-	SMD 2.18 higher (1.22 higher to 3.14 higher)	⊕○○○ Very Low
FAS						1				
8	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	333	1841	-	SMD 2.83 higher (2.14 higher to 3.53 higher)	⊕○○○ Very Low
pFAS										
8	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	245	1846	-	SMD 2.07 higher (1.70 higher to 2.43 higher)	⊕○○○ Very Low
ARND/O	thers									
4	serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>e</sup>	none	195	1310	-	SMD 0.43 higher (0.12 higher to 0.74 higher)	⊕○○○ Very Low

Notes: CI: confidence interval; MD: mean difference; SMD: standard 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.

# Meta-analyses for dysmorphology checklist

# Exposure studies

	Mode	rate P	AE	Co	Control			td. 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	
3andoli et al 2020*	5.1	5.7	45	2.5	2.6	253	100.0%	0.80 [0.47, 1.12]		•	
otal (95% CI)			45			253	100.0%	0.80 [0.47, 1.12]	•		
leterogeneity: Not ap	pplicable							+			
Fest for overall effect	: Z = 4.83	(P ≤ 0.	00001	)				-	Control Moderate PAE		
									Control incoordio l'Ale		
Diele of high lange of											
KISK OF DIAS legend											
		V	ery He	eavy P	AE a	nd Dy	smorph	ology Score (m/SD)	(2 studies)		
<u>Risk of bias legend</u> ( <b>A</b> ) Overall RoB	Very H	Ve leavy f		•	AE a		•	ology Score (m/SD) Std. Mean Difference	(2 studies) Std. Mean Difference	Risk of Bias	
(A) Overall RoB	Very H Mean			C				•••••••••••••••••••••••••••••••••••••••		Risk of Bias A	
	-	leavy F	PAE	С	ontro	Total	Weight	Std. Mean Difference	Std. Mean Difference		
(A) Overall RoB	Mean	leavy F SD	PAE Total	C Mean	ontro SD 2.6	Total 253	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference		
A) Overall RoB Study or Subgroup Bandoli et al 2020*	Mean 7.3	leavy F SD 8.7	PAE Total 19	C Mean 2.5	ontro SD 2.6	Total 253	Weight 58.1% 41.9%	Std. Mean Difference IV, Random, 95% CI 1.42 [0.94, 1.90]	Std. Mean Difference		

Risk of bias legend (A) Overall RoB

Notes: \* indicates used a total dysmorphology score other than Hoyme 2005. Bandoli et al 2020 reports multiple trajectories, used Trajectory D (90g/week) for Moderate PAE Trajectory E (313g/week) for Very Heavy PAE.

# Diagnosed studies

			F	ASD a	nd D	ysmo	rpholog	y Score (3 studies)			
FASD					ontrol		:	Std. Mean Difference	Std. Mear	Risk of Bias	
Study or Subgroup	group Mean		lean SD Total		Mean SD To		Weight	IV, Random, 95% CI	IV, Rand	Α	
Kodituwakku et al 2006b	12.4	3.88	22	3.3	3.09	60	33.8%	2.72 [2.07, 3.37]			?
Kalberg et al 2013	17.1	4.5	61	5.2	4.3	52	35.8%	2.68 [2.17, 3.19]		<b> </b> − <b>∎</b> −	•
May et al 2021*	9.2	2.6	6	5.4	3.9	71	30.4%	0.98 [0.13, 1.83]			•
Total (95% CI)			89			183	100.0%	2.18 [1.22, 3.14]		•	
Heterogeneity: Tau <sup>2</sup> = 0.60 Test for overall effect: Z = 4	•			P = 0.00	02); I <sup>z</sup> =	= 84%			-4 -2 Contro	0 2 · I FASD	<u>↓</u> 4

#### Risk of bias legend (A) Overall RoB

		C	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias		
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Α
Coles et al 2002*	7.02	6.14	46	2.62	3.16	53	13.0%	0.91 [0.50, 1.33]		•
Hasken et al 2021	18	3.8	96	7.2	4.1	331	13.3%	2.67 [2.38, 2.96]		•
May et al 2000*	10.7	4.47	46	2.3	2.56	42	12.6%	2.26 [1.72, 2.80]		•
May et al 2007	18.4	3.3	55	8.1	4.19	145	13.0%	2.59 [2.18, 2.99]	-	•
May et al 2015	13.3	4.65	7	4.1	3.18	190	11.5%	2.83 [2.03, 3.64]	· · · ·	•
May et al 2020b*	15.8	3.8	8	4.4	3.1	413	11.8%	3.66 [2.91, 4.40]		•
May et al 2020c*	16.7	3	11	4.2	2.9	521	12.1%	4.30 [3.65, 4.95]		- 😑
Viljoen et al 2005	14	4.31	64	2.2	2.68	146	12.8%	3.61 [3.15, 4.06]	-	•
Total (95% CI)			333			1841	100.0%	2.83 [2.14, 3.53]	•	
Heterogeneity: Tau <sup>2</sup> =	: 0.93° CI	hi <sup>z</sup> = 1 <sup>-</sup>	17.92	df = 7 (P	, < 0 0i	0001\.	<sup>2</sup> = 94%		-+ · · · · · ·	
Test for overall effect:						,,, .			-4 -2 0 2 4 Control FAS	

# pFAS and Dysmorphology Score (8 studies)

	1	<b>FAS</b>		С	ontrol			Std. Mean Difference	Std. Mear	Difference	Risk of Bias
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Rand	om, 95% Cl	Α
Aragon et al 2008b (FAS/pFAS)	12.91	3.39	24	4.26	2.56	32	9.5%	2.90 [2.13, 3.67]			- ?
May et al 2010 - Italian Cohort (FAS/pFAS)	12	4.05	39	4.4	3.43	179	13.7%	2.14 [1.73, 2.54]			?
Coles et al 1997* (FAS/pFAS)	7.24	4.64	25	2.09	2.08	35	11.6%	1.50 [0.92, 2.09]		<b>→</b>	•
Hasken et al 2021	12.9	3.6	81	7.2	4.1	331	15.1%	1.42 [1.16, 1.68]			•
May et al 2007	17.8	3.92	18	8.1	4.19	145	12.0%	2.32 [1.77, 2.87]		_ <b>_</b>	•
May et al 2015	11.3	3.92	19	4.1	3.8	190	12.5%	1.88 [1.38, 2.39]		_ <b>_</b>	•
May et al 2020b*	10.8	3.1	16	4.4	3.1	413	12.4%	2.06 [1.54, 2.58]		<b>→</b>	•
May et al 2020c*	11.8	3.6	23	4.2	2.9	521	13.2%	2.59 [2.14, 3.03]		-	•
Total (95% CI)			245			1846	100.0%	2.07 [1.70, 2.43]		•	
Heterogeneity: Tau <sup>2</sup> = 0.21; Chi <sup>2</sup> = 34.30, df	= 7 (P <	0.000	1); <b>I<sup>2</sup> =</b> 8	30%					L L		÷
Test for overall effect: Z = 11.07 (P < 0.0000	1)								-4 -2 Contro	U 2 I pFAS	4

Risk of bias legend (A) Overall RoB

ARND/Others and Dysmorphology Score (6 studies)

	ARND/Others Control							Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	Α
Coles et al 2002* (non-syndromal)	3.12	3.44	82	2.62	3.16	53	27.4%	0.15 [-0.20, 0.50]		•
Hasken et al 2021 (ARND)	10	3.3	78	7.2	4.1	331	32.7%	0.71 [0.45, 0.96]		•
May et al 2020b* (ARND)	5.2	3.9	25	4.4	3.1	413	24.4%	0.25 [-0.15, 0.66]	+ <b>-</b> -	•
May et al 2020c* (ARND)	6.1	4.3	10	4.2	2.9	521	15.5%	0.65 [0.02, 1.27]		•
Total (95% CI)			195			1318	100.0%	0.43 [0.12, 0.74]	•	
Heterogeneity: Tau² = 0.06; Chi² = 8.1 Test for overall effect: Z = 2.73 (P = 0	-	(P = 0	).04); I²	= 63%					-4 -2 0 2 4 Control ARND/Others	 ,

Risk of bias legend

(A) Overall RoB

*Note:* Non-marked papers used the total dysmorphology score by Hoyme 2005. \* indicates used a total dysmorphology score other than Hoyme 2005. Coles et al 1985 reports neonatal and follow-up (~15yrs), used 15yrs in meta-analysis. Coles et al 1997 reports neonatal and follow-up (~8yrs), used 8yrs for meta-analysis. Hasken et al 2021 also reports non-syndromal.