

Supplemental File E

GRADE ratings and meta-analyses for dysmorphology outcomes

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Summary of available outcomes for 3 sentinel facial features

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

	Certainty assessment					№ of patients		Effect		Certainty
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
PHILTRUM MEASURES										
Philtrum Smoothness (3 or 4+) (%)										
Moderate PAE (3+)										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	45	253	OR 3.26 (1.36 to 7.82)	-	⊕⊕○○ Low
Very Heavy PAE (3+)										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	19	253	OR 6.03 (2.05 to 17.74)	-	⊕⊕○○ Low
Confirmed unquantifiable (4+)										
3	serious ^a	not serious	not serious	serious ^{e,f}	none	174/344 (50.6%)	43/316 (13.6%)	OR 6.24 (4.22 to 9.22)	360 more per 1,000 (from 263 more to 456 more)	⊕⊕○○ Low
Philtrum Rank (1-5) (m/SD)										
Confirmed unquantifiable										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	65	55	-	SMD 0.7 higher (0.33 higher to 1.07 higher)	⊕⊕○○ Low
Philtrum Length (mm) (m/SD)										
Heavy										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	16	48	-	SMD 1.34 higher (0.73 higher to 1.96 higher)	⊕⊕○○ Low
Long Philtrum (%)										
Moderate										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	7/45	20/253	OR 2.15 (0.85 to 5.42)	-	⊕○○○ Very Low
Very Heavy										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	19	253	OR 2.18 (0.59 to 8.14)	-	⊕○○○ Very Low
Hypoplastic Philtrum (%)										
Any PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	12	12	OR 18.33 (0.88 to 380.70)	-	⊕○○○ Very Low
VERMILION MEASURES										
Vermilion Thinness (3 or 4+) (%)										
Moderate PAE (3+)										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	11/45	40/253	OR 1.72 (0.81 to 3.68)	-	⊕○○○ Very Low
Very Heavy PAE (3+)										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	6/19	40/253	OR 2.46 (0.88 to 6.85)	-	⊕○○○ Very Low
Confirmed unquantifiable (4+)										
3	serious ^a	not serious	not serious	serious ^f	none	162/334 (48.5%)	46/316 (14.6%)	OR 5.28 (3.6 to 7.74)	328 more per 1,000 (from 235 more to 423 more)	⊕⊕○○ Low
Vermilion Rank (1-5) (m/SD)										

10	serious ^a	serious ^b	not serious	serious ^e	none	299/357 (83.75%)	505/248 8 (20.20%)	OR 19.22 (11.00 to 33.56)	-	⊕○○○ Very Low
ARND/Others										
9	serious ^a	serious ^b	not serious	serious ^d	none	107/456 (23.5%)	380/217 5 (17.5%)	OR 1.22 (0.74 to 2.00)	31 more per 1,000 (from 39 fewer to 123 more)	⊕○○○ Very low
Philtrum Rank (1-5) (%) (m/SD)										
FASD Diagnosis										
3	serious ^a	not serious	not serious	serious ^{e,f}	none	108	94	-	SMD 0.53 higher (0.26 higher to 0.80 higher)	⊕⊕○○ Low
Philtrum Length (mm) (m/SD)										
FASD										
2	serious ^a	serious ^b	not serious	very serious ^{d,e,f}	none	43	150	-	MD 0.08 higher (1.78 lower to 1.94 higher)	⊕○○○ Very low
FAS										
3	serious ^a	not serious	serious ^c	serious ^{d,e}	none	187	381	-	MD 0.27 higher (0.26 lower to 0.79 higher)	⊕○○○ Very low
pFAS										
3	serious ^a	not serious	serious ^c	serious ^{d,e}	none	105	284	-	MD 0.52 higher (0.21 lower to 1.25 higher)	⊕○○○ Very low
ARND/Others										
2	serious ^a	serious ^b	serious ^c	very serious ^{d,e,f}	none	76	139	-	MD 1.77 higher (0.16 lower to 3.71 higher)	⊕○○○ Very low
Long Philtrum (%)										
Any FASD Diagnosis										
3	serious ^a	not serious	not serious	not serious	none	191	519	OR 1.68 (1.17 to 2.41)	-	⊕⊕⊕○ Moderate
'Other' Philtrum measures – Philtrum Length (z-score), Philtrum Depth (mm)										
FASD – Philtrum Length (z-score)										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	40	31	-	MD 0.07 lower (0.54 lower to 0.40 higher)	⊕○○○ Very low
FASD – Philtrum Depth (mm)										
1	serious ^a	not serious	not serious	serious ^f	none	25	30	-	MD 0.36 lower (0.50 lower to 0.22 lower)	⊕⊕○○ Low
VERMILION MEASURES										
Vermilion Thinness (4+) (%)										
FASD										
5	serious ^a	serious ^b	not serious	serious ^{e,f}	none	87/170 (51.2%)	44/272 (16.2%)	OR 10.10 (4.09 to 24.9)	499 more per 1,000 (from 279 more to 666 more)	⊕○○○ Very low
FAS										
12	serious ^a	serious ^b	not serious	serious ^e	none	421/511 (82.38%)	468/263 4 (17.76%)	OR 21.72 (12.07 to 39.08)	-	⊕○○○ Very low
pFAS										

FASD										
5	serious ^a	serious ^b	not serious	not serious	none	188	264	-	MD 1.3 lower (2.08 lower to 0.52 lower)	⊕⊕○○ Low
FAS										
5	serious ^a	serious ^b	serious ^c	not serious	none	272	601	-	MD 2.15 lower (2.73 lower to 1.57 lower)	⊕○○○ Very low
pFAS										
4	serious ^a	serious ^b	serious ^c	not serious	none	124	374	-	MD 1.43 lower (1.88 lower to 0.97 lower)	⊕○○○ Very low
ARND/Others										
2	serious ^a	serious ^b	serious ^c	serious ^{d,f}	none	76	139	-	MD 0.27 lower (0.86 lower to 0.31 higher)	⊕○○○ Very low
Palpebral Fissure Length (Centiles)										
FASD										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	6	71	-	MD 15.90 lower (31.41 lower to 0.21 higher)	⊕○○○ Very low
FAS										
5	serious ^a	not serious	not serious	not serious	none	124	2286	-	MD 19.31 lower (21.30 lower to 17.33 lower)	⊕⊕⊕○ Moderate
pFAS										
6	serious ^a	serious ^b	not serious	not serious	none	210	2318	-	MD 19.06 lower (27.08 lower to 11.03 lower)	⊕⊕○○ Low
ARND/Others										
5	serious ^a	not serious	not serious	serious ^d	none	169	2286	-	MD 0.84 lower (4.44 lower to 2.76 higher)	⊕⊕○○ Low
Palpebral Fissure Length (z-scores)										
FAS										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	41	31	-	MD 1.37 lower (2.02 lower to 0.72 lower)	⊕⊕○○ Low
pFAS										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	79	47	-	MD 0.98 lower (2.27 lower to 0.31 higher)	⊕○○○ Very low
ARND/Others										
1	serious ^a	not serious	not serious	serious ^{e,f}	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.

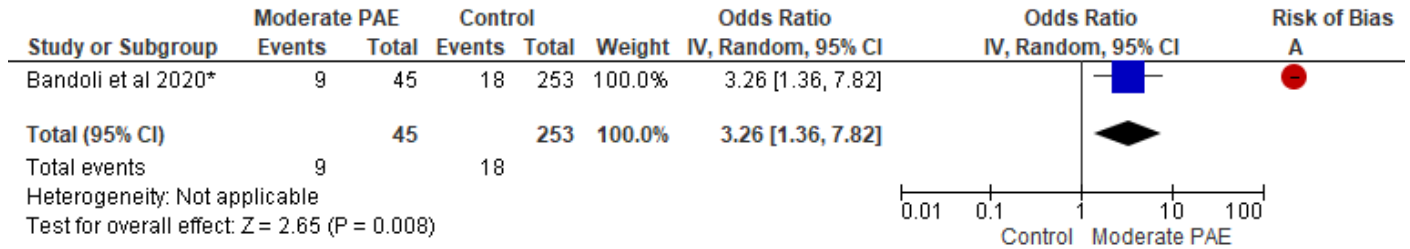
Meta-analyses for 3 sentinel facial features

Exposure studies

PHILTRUM OUTCOMES

Frequency of Philtrum Smoothness (3 or 4+) (%)

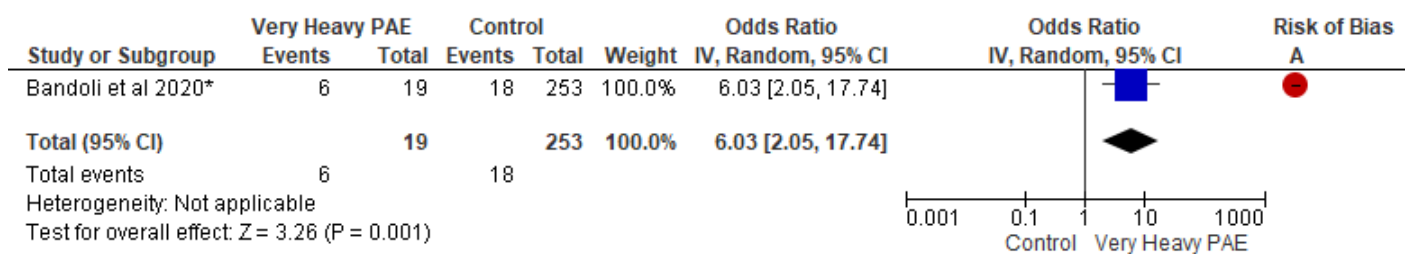
Moderate PAE and Philtrum Smoothness (3+) (1 study)



Risk of bias legend

(A) RoB

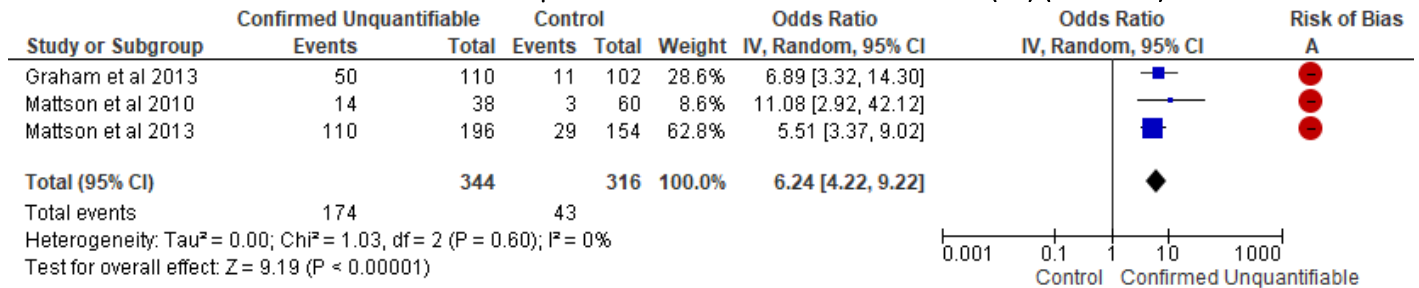
Very Heavy PAE and Philtrum Smoothness (3+) (1 study)



Risk of bias legend

(A) RoB

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



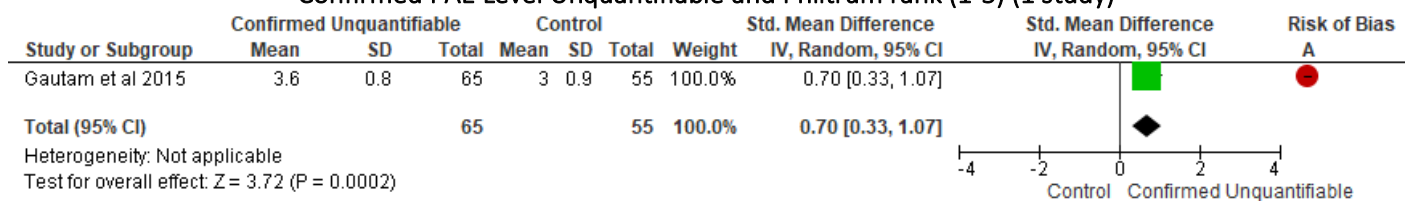
Risk of bias legend

(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 PAE Level Unquantifiable and Philtrum rank (1-5) (1 study)

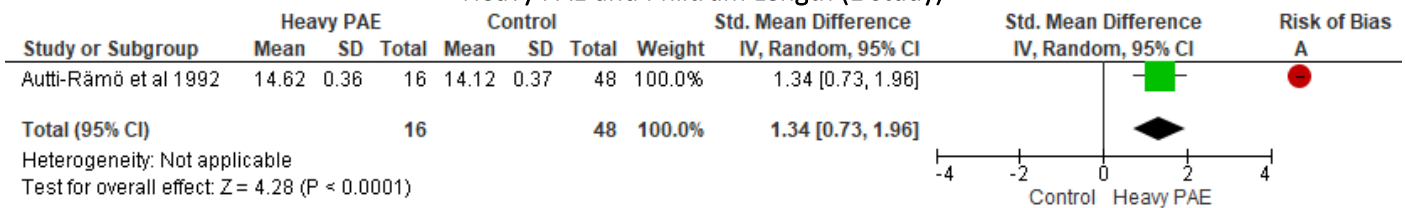


Risk of bias legend

(A) RoB

Philtrum Length (mm) (m/SD)

Heavy PAE and Philtrum Length (1 study)



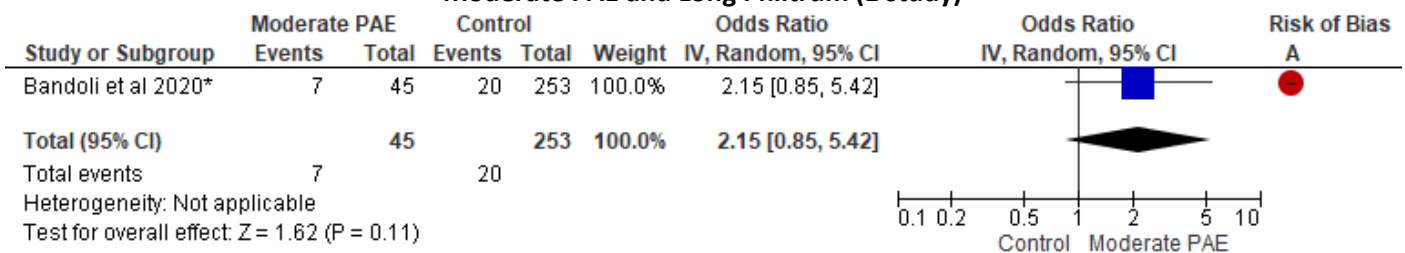
Risk of bias legend

(A) RoB

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

Long Philtrum (%)

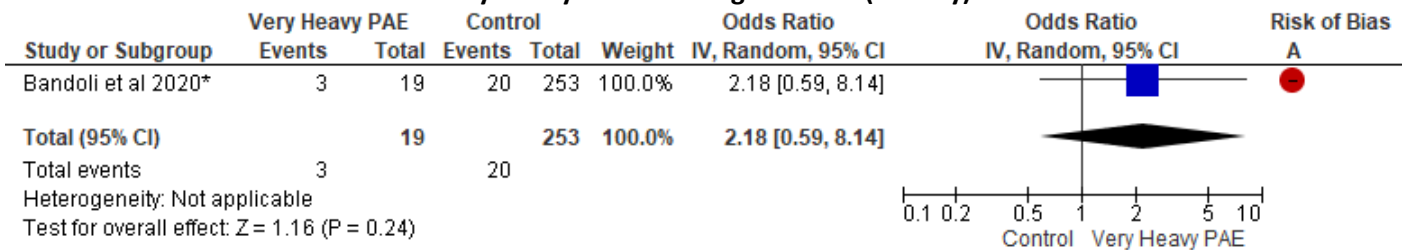
Moderate PAE and Long Philtrum (1 study)



Risk of bias legend

(A) RoB

Very Heavy PAE and Long Philtrum (1 study)



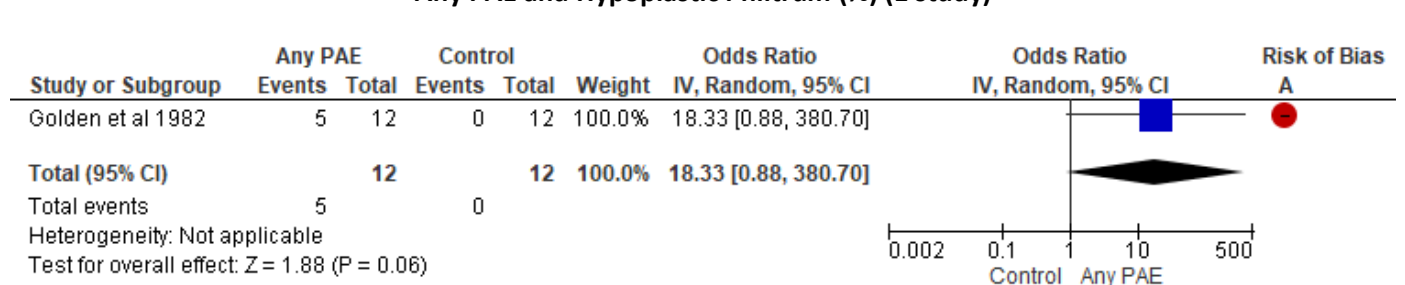
Risk of bias legend

(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)



Risk of bias legend

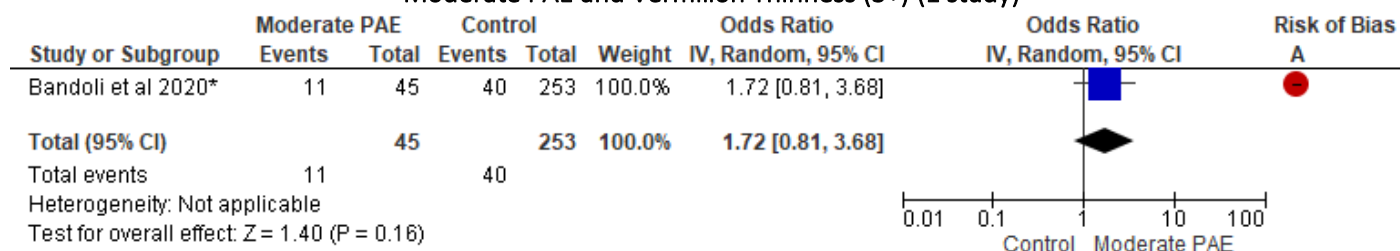
(A) RoB

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

VERMILION OUTCOMES

Vermilion Thinness (3 or 4+) (%)

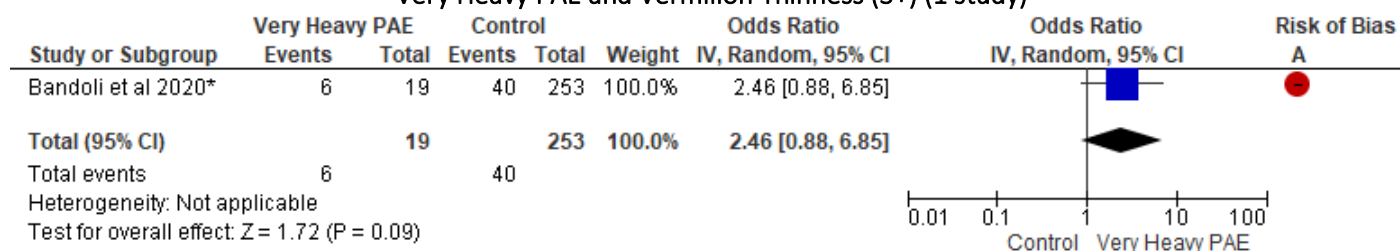
Moderate PAE and Vermilion Thinness (3+) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

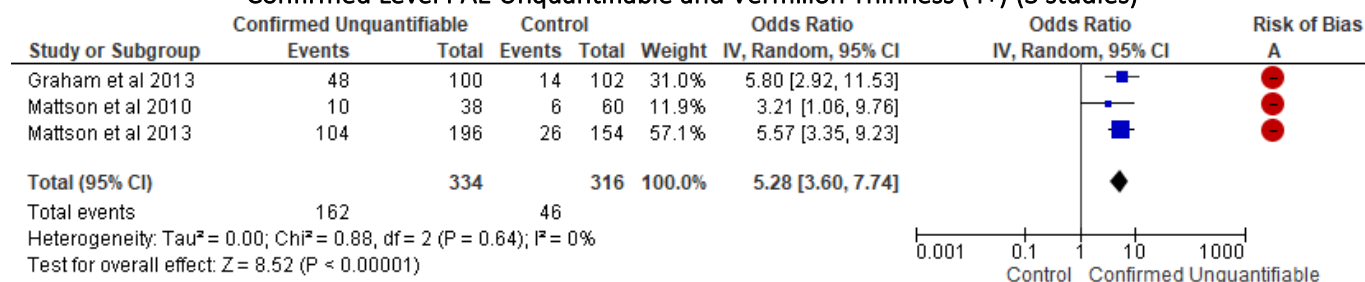
Very Heavy PAE and Vermilion Thinness (3+) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

Confirmed Level PAE Unquantifiable and Vermilion Thinness (4+) (3 studies)



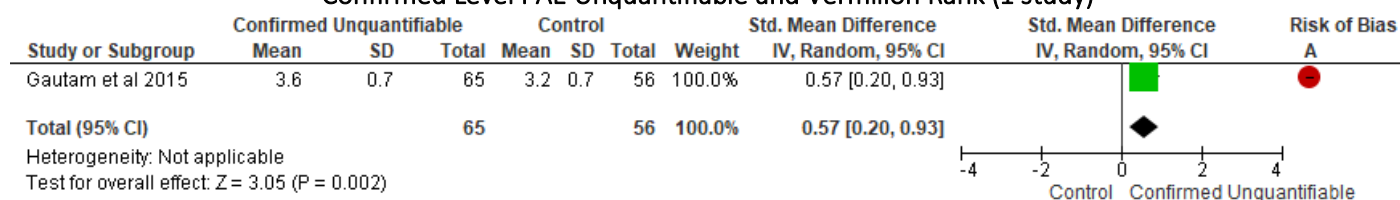
[Risk of bias legend](#)

(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)

Confirmed Level PAE Unquantifiable and Vermilion Rank (1 study)

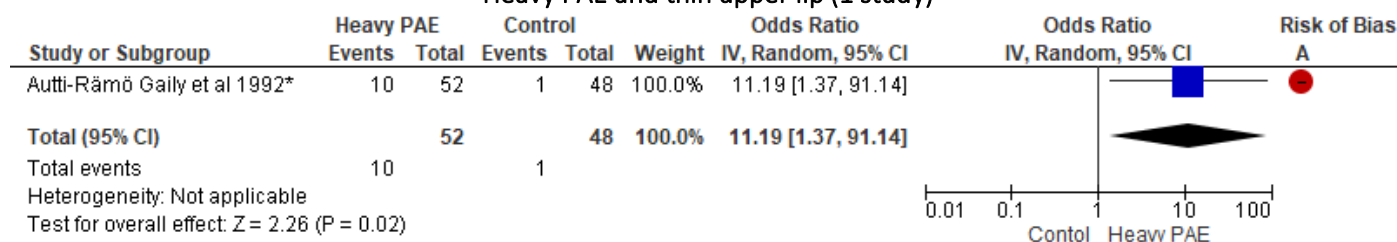


[Risk of bias legend](#)

(A) Overall RoB

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

Heavy PAE and thin upper lip (1 study)

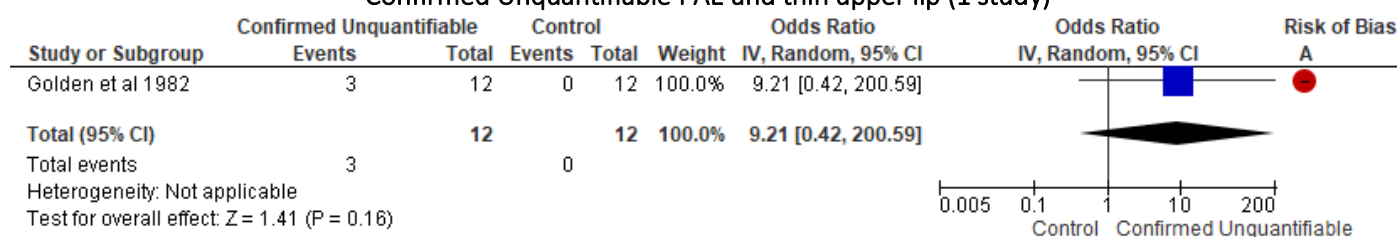


Risk of bias legend

(A) Overall RoB

Notes: Thin Upper Lip defined by Jones et al 1988

Confirmed Unquantifiable PAE and thin upper lip (1 study)



Risk of bias legend

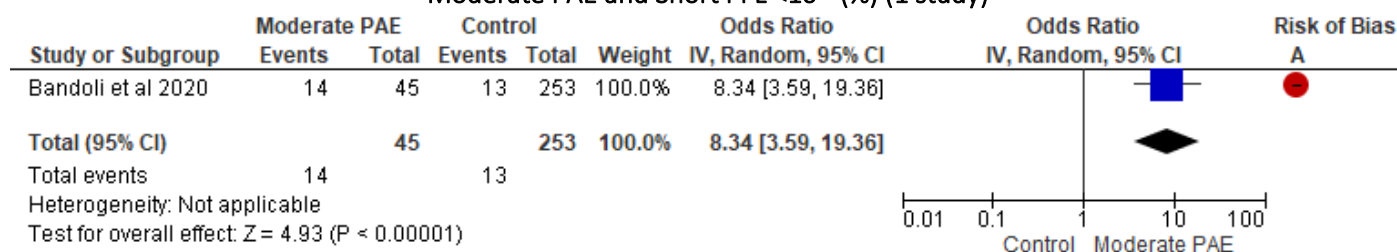
(A) Overall RoB

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

PALPEBRAL FISSURE MEASURES

Frequency of Short Palpebral Fissures (<3rd or <10th percentile)

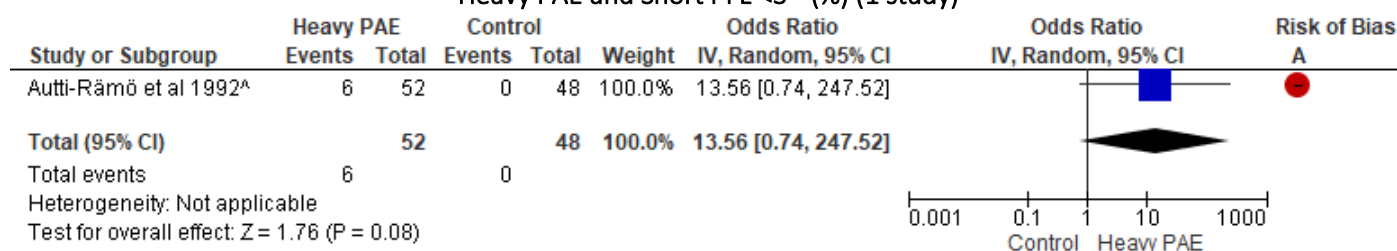
Moderate PAE and Short PFL <10th (%) (1 study)



Risk of bias legend

(A) Overall RoB

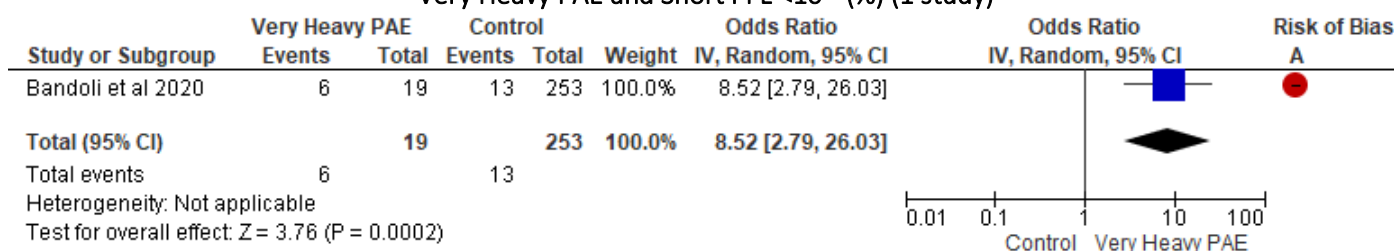
Heavy PAE and Short PFL <3rd (%) (1 study)



Risk of bias legend

(A) Overall RoB

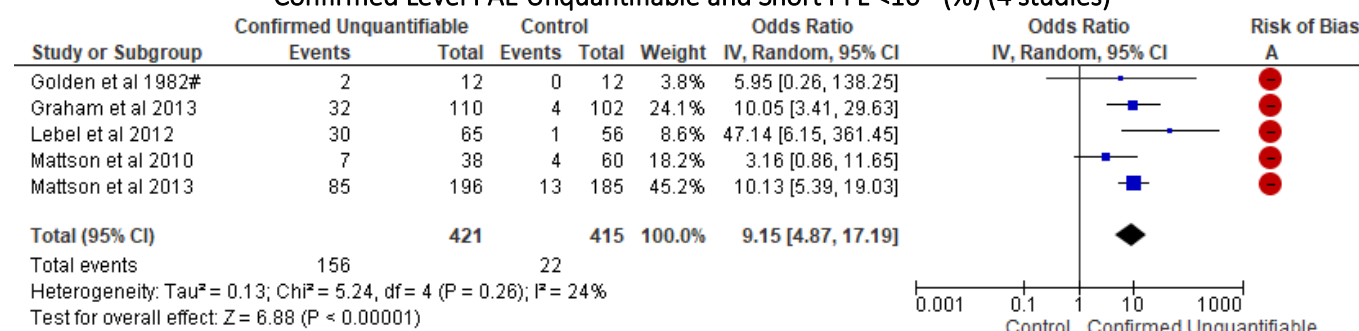
Very Heavy PAE and Short PFL <10th (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



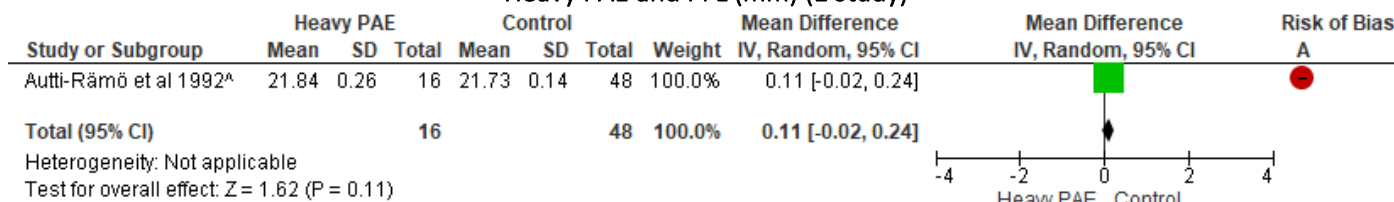
Risk of bias legend

(A) Overall RoB

Notes: Unmarked studies do not report norms. All studies define short PFL <10th 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)

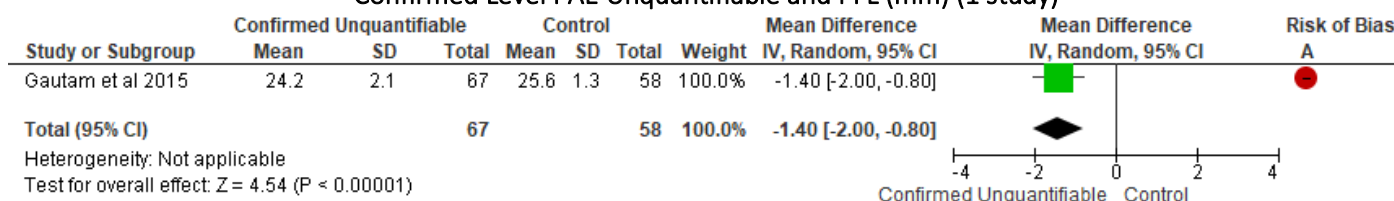
Heavy PAE and PFL (mm) (1 study)



Risk of bias legend

(A) Overall RoB

Confirmed Level PAE Unquantifiable and PFL (mm) (1 study)



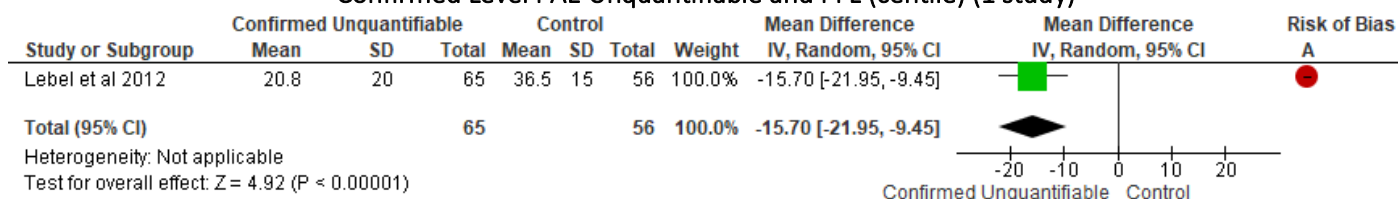
Risk of bias legend

(A) Overall RoB

Notes: Autti-Rämö 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 Unquantifiable and PFL (centile) (1 study)



[Risk of bias legend](#)

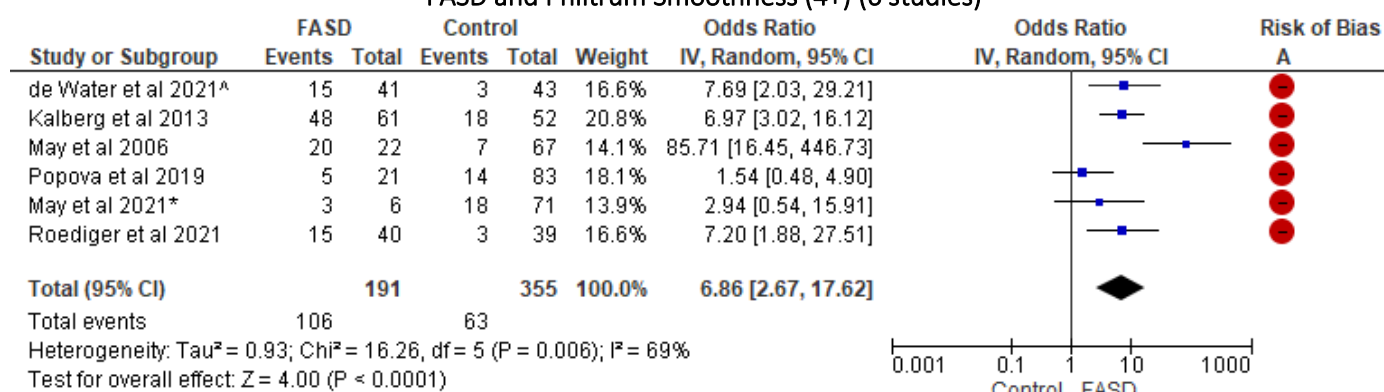
(A) Overall RoB

Diagnosed studies

PHILTRUM MEASURES

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

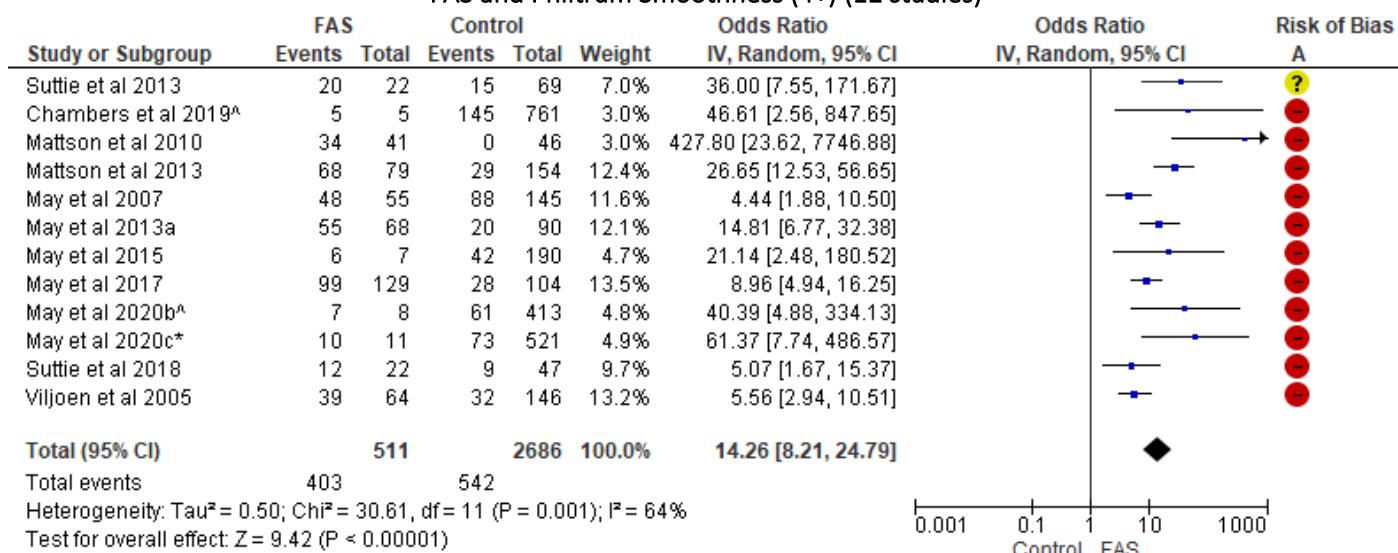
FASD and Philtrum Smoothness (4+) (6 studies)



[Risk of bias legend](#)

(A) RoB

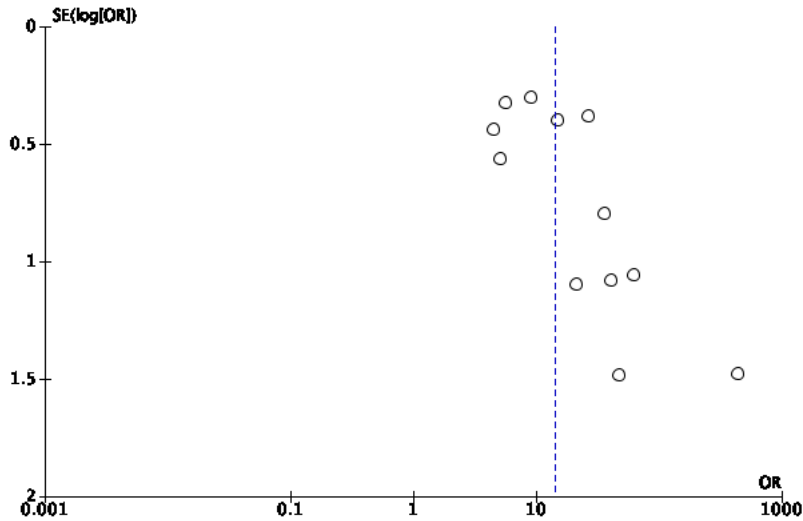
FAS and Philtrum Smoothness (4+) (12 studies)



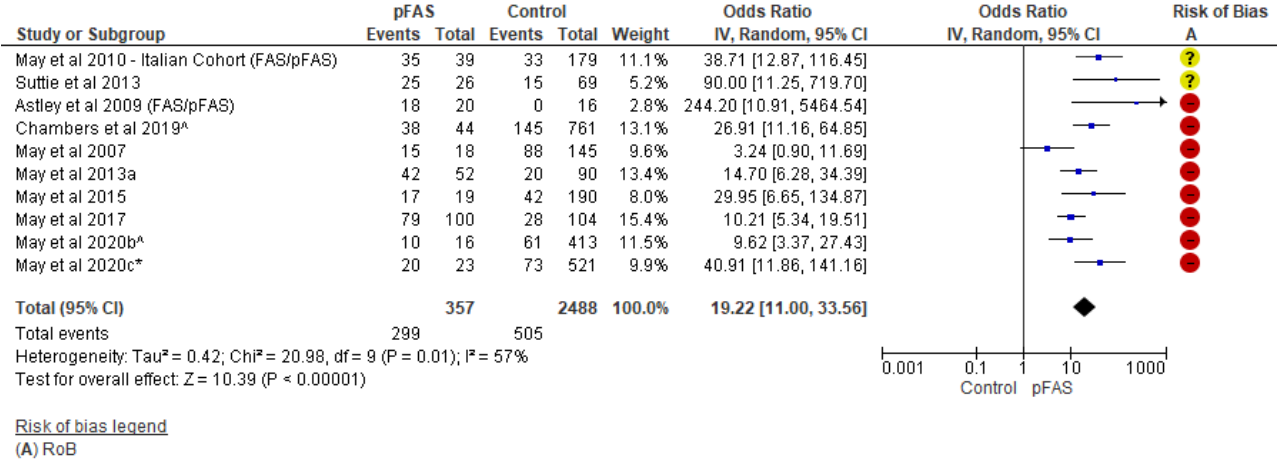
[Risk of bias legend](#)

(A) RoB

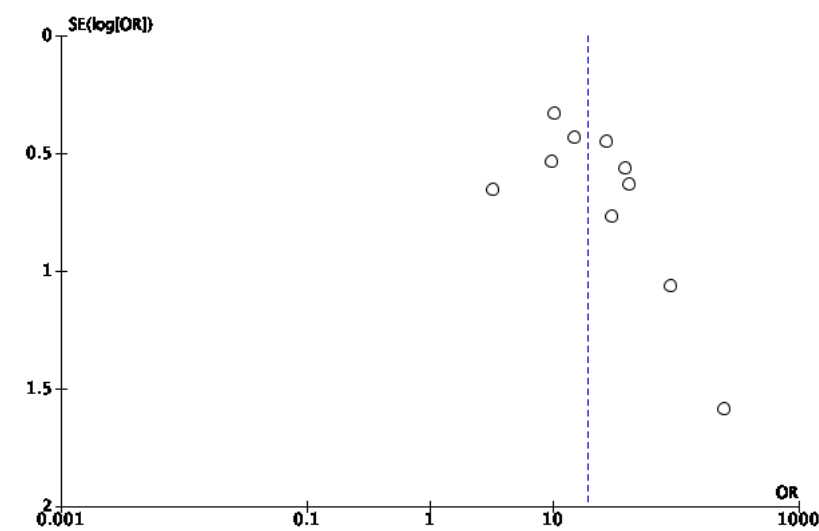
Funnel Plot: FAS diagnosis and Philtrum Smoothness (4+)



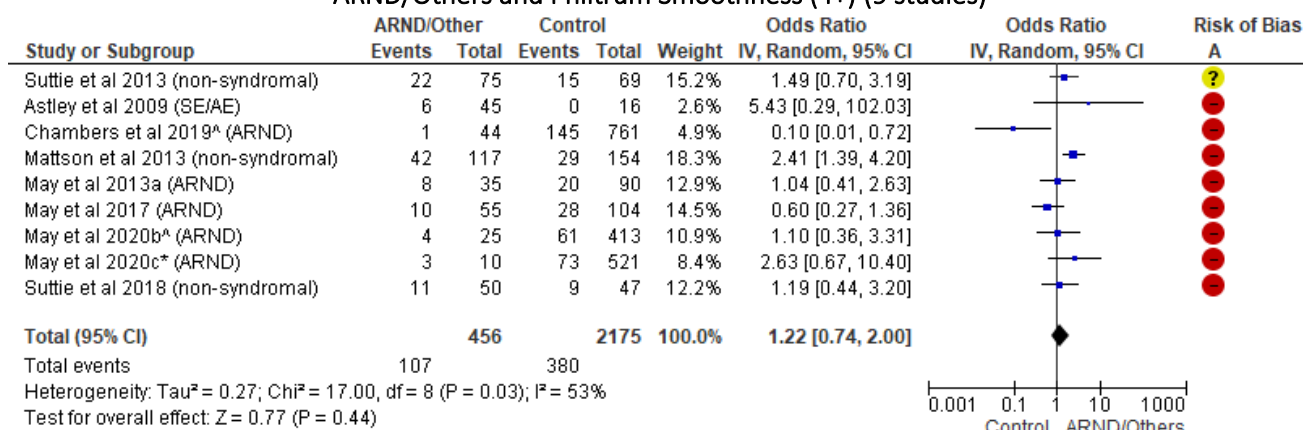
pFAS and Philtrum Smoothness (4+) (10 studies)



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



ARND/Others and Philtrum Smoothness (4+) (9 studies)



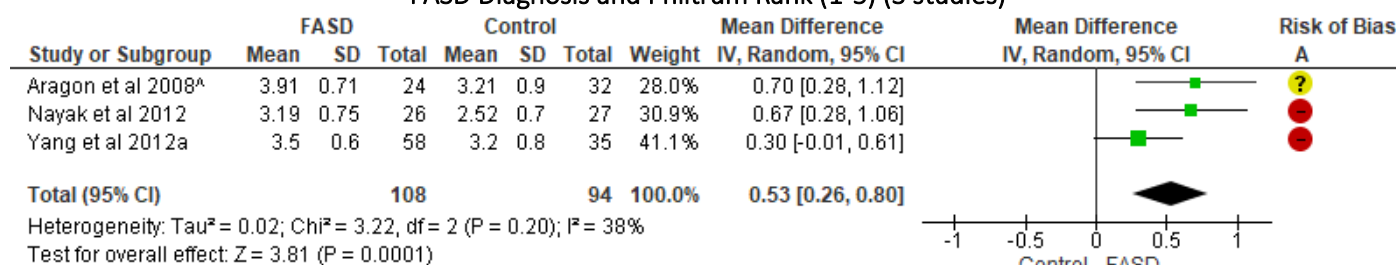
Risk of bias legend

(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)

FASD Diagnosis and Philtrum Rank (1-5) (3 studies)



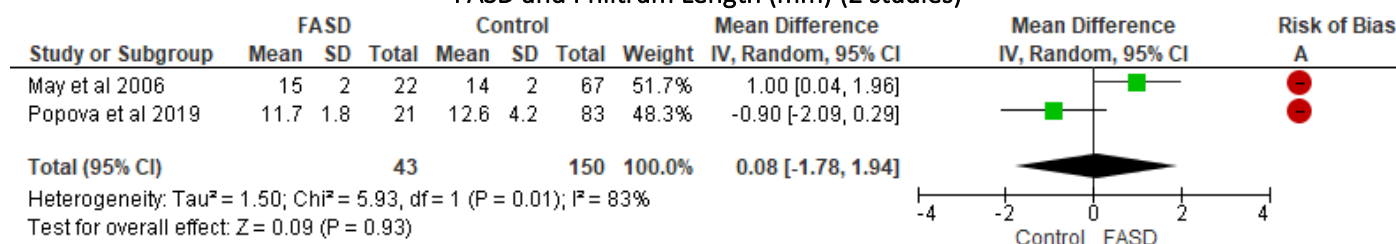
Risk of bias legend

(A) RoB

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

Philtrum Length (mm) (m/SD)

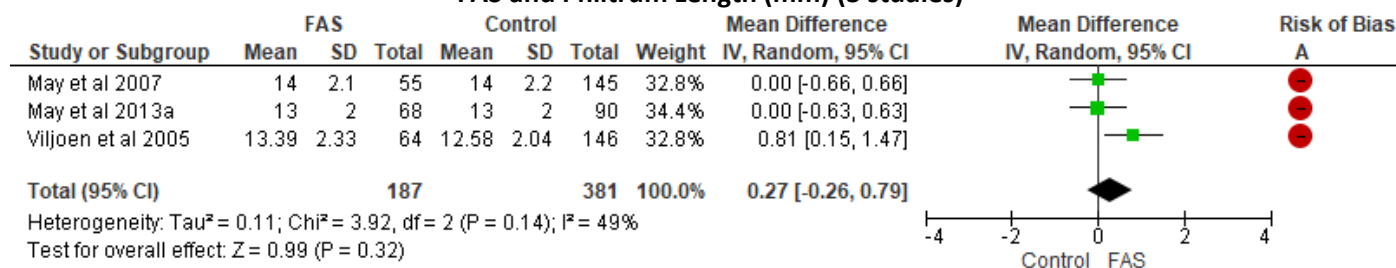
FASD and Philtrum Length (mm) (2 studies)



Risk of bias legend

(A) RoB

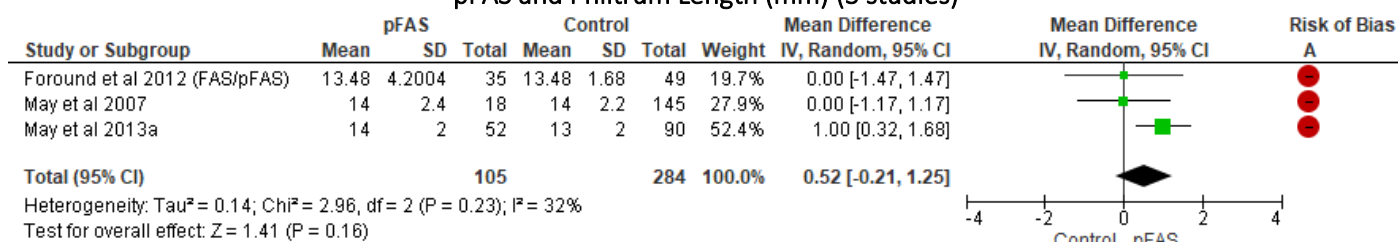
FAS and Philtrum Length (mm) (3 studies)



Risk of bias legend

(A) RoB

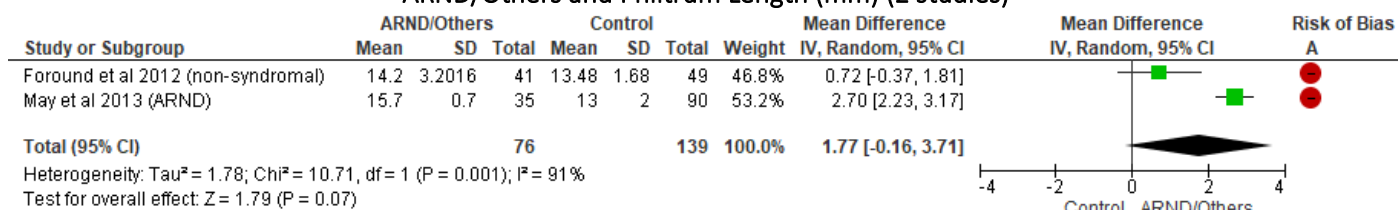
pFAS and Philtrum Length (mm) (3 studies)



[Risk of bias legend](#)

(A) RoB

ARND/Others and Philtrum Length (mm) (2 studies)



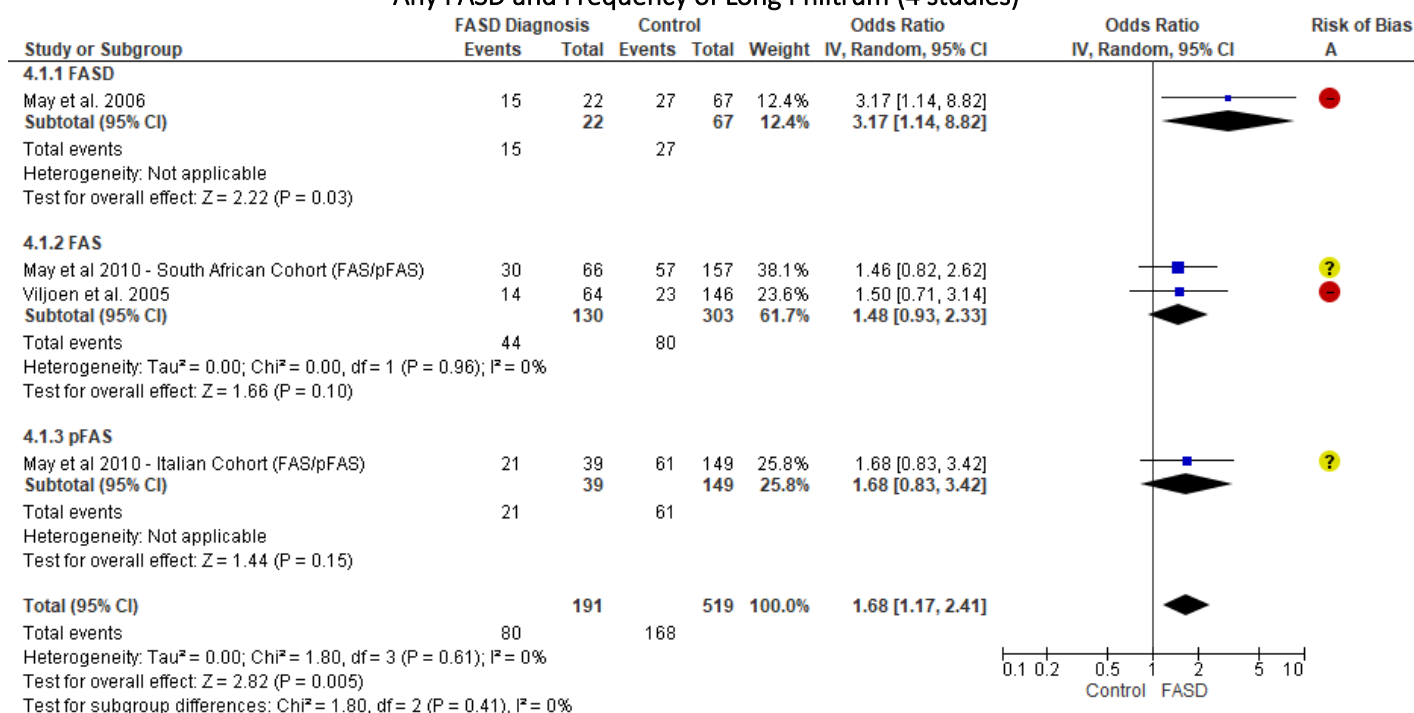
[Risk of bias legend](#)

(A) RoB

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

Long Philtrum (%)

Any FASD and Frequency of Long Philtrum (4 studies)



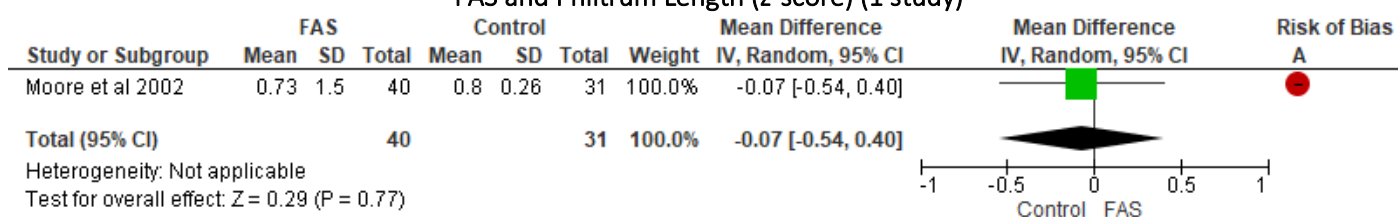
[Risk of bias legend](#)

(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 and Philtrum Length (z-score) (1 study)

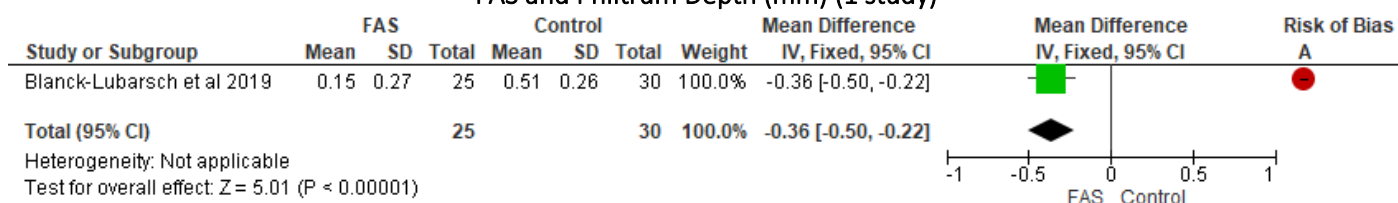


[Risk of bias legend](#)

(A) RoB

Note: Moore et al 2002 also reported pFAS.

FAS and Philtrum Depth (mm) (1 study)



Risk of bias legend

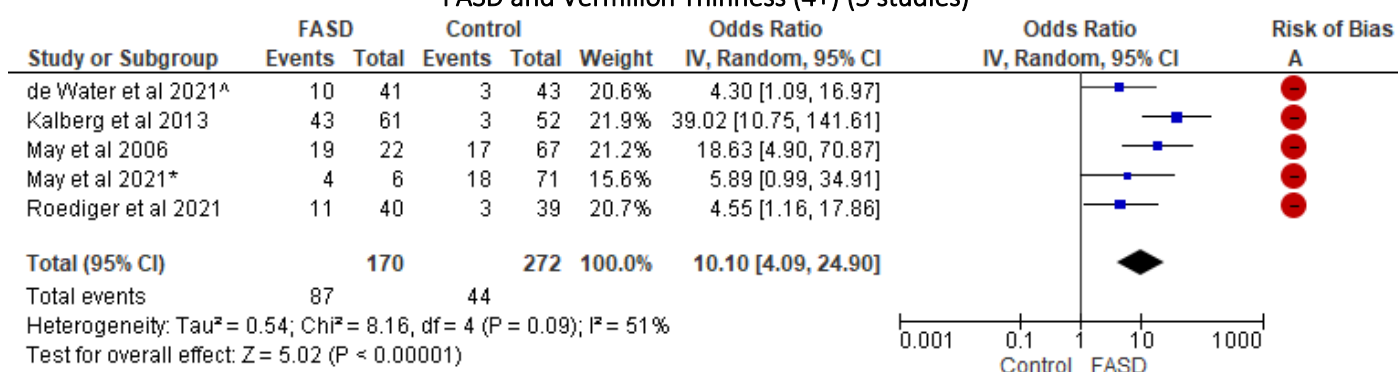
(A) RoB

Note: Blanck-Lubarsch et al 2019b

VERMILION MEASURES

Frequency of Vermilion Thinness (4+) (%)

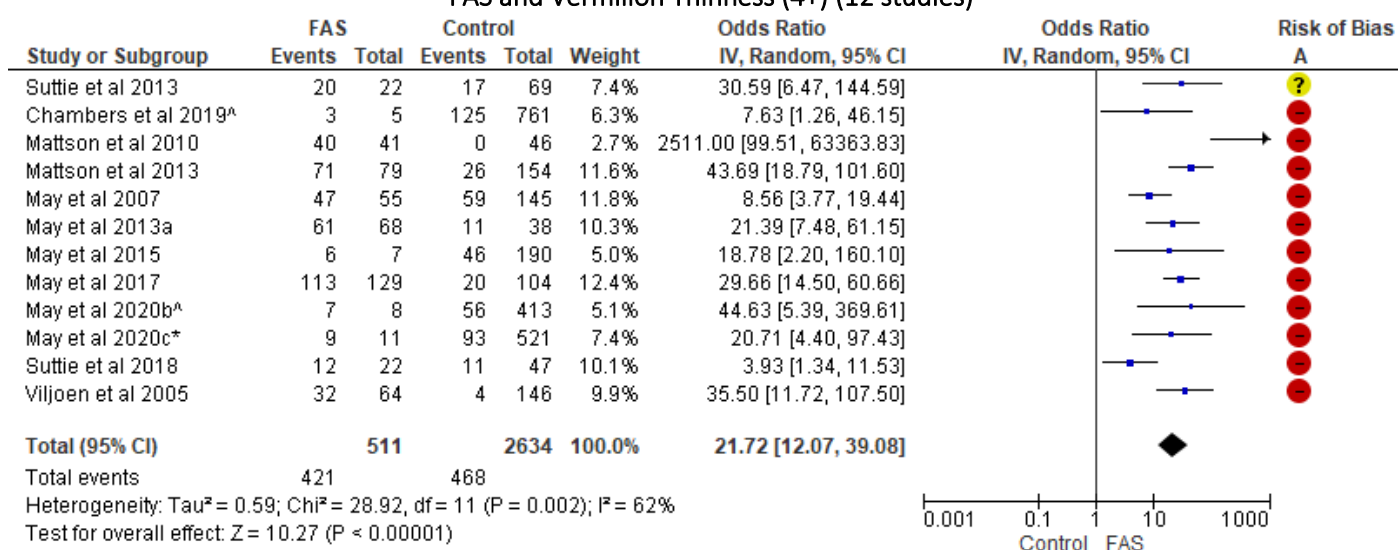
FASD and Vermilion Thinness (4+) (5 studies)



Risk of bias legend

(A) Overall RoB

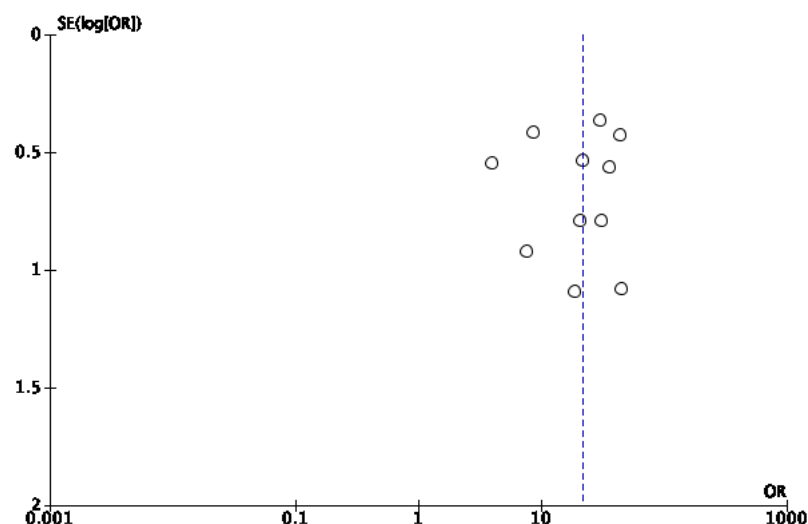
FAS and Vermilion Thinness (4+) (12 studies)



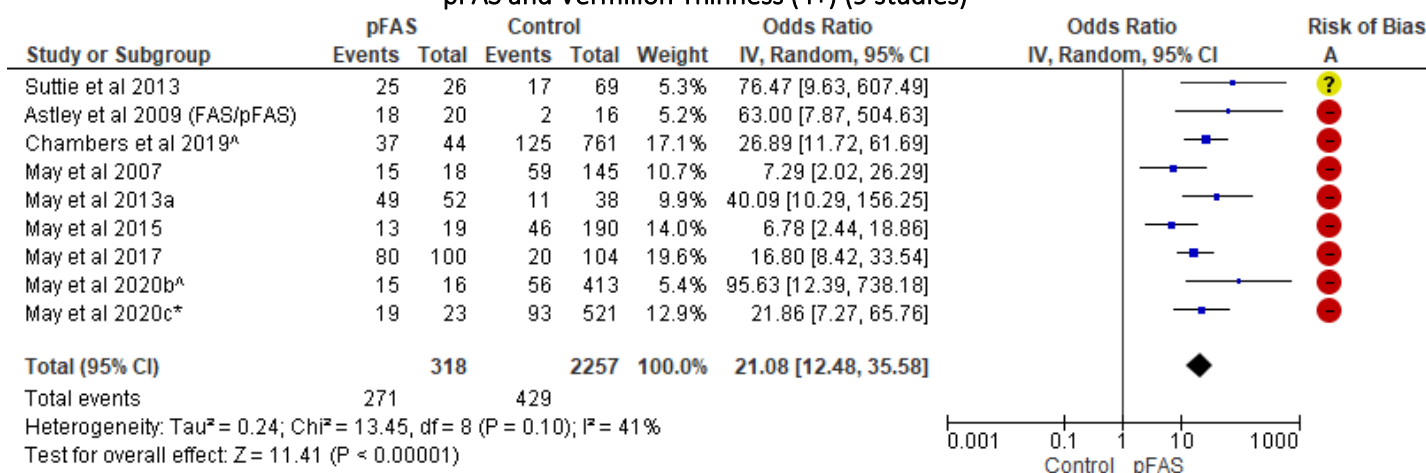
Risk of bias legend

(A) Overall RoB

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

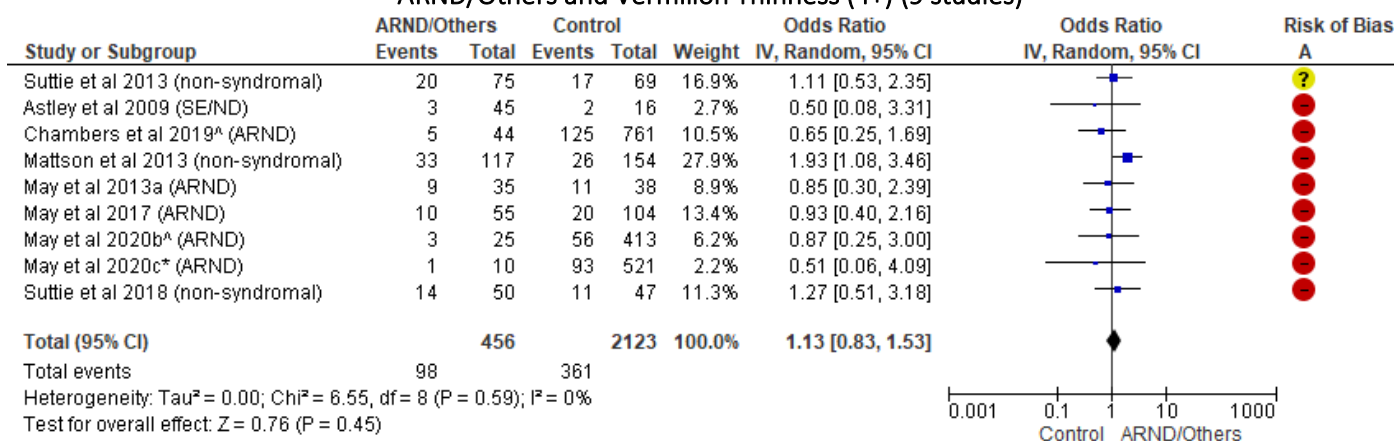


pFAS and Vermilion Thinness (4+) (9 studies)

Risk of bias legend

(A) Overall RoB

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

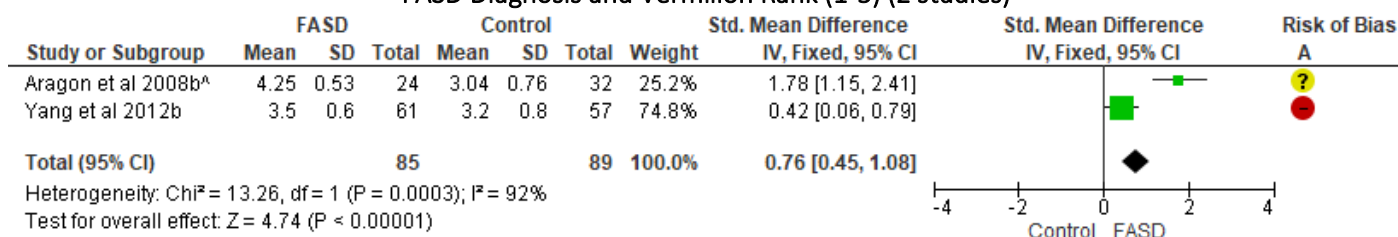
Risk of bias legend

(A) Overall RoB

Notes: ^a 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)



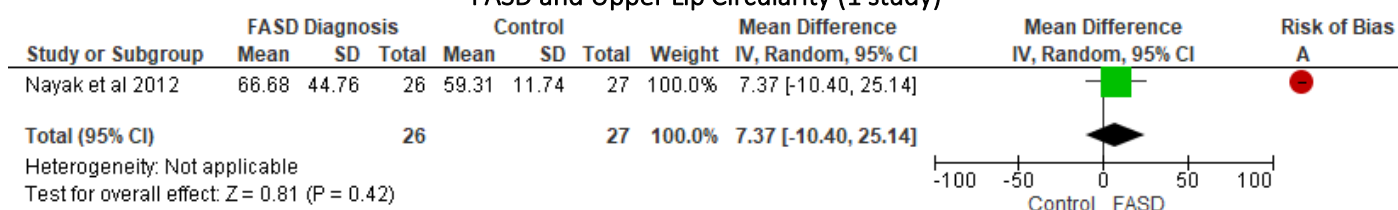
Risk of bias legend

(A) Overall RoB

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

Upper Lip Circularity (m/SD)

FASD and Upper Lip Circularity (1 study)



Risk of bias legend

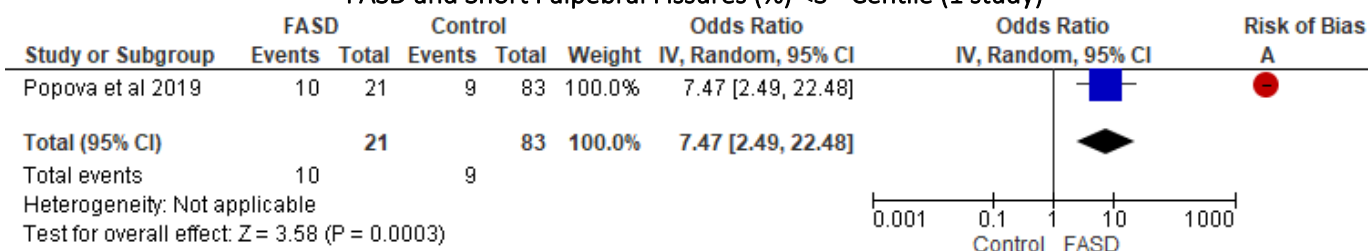
(A) Overall RoB

Notes: Upper lip circularity as defined by Astley 2000.

PALPEBRAL FISSURE MEASURES

Frequency of Short Palpebral Fissures (%) <3rd Centile

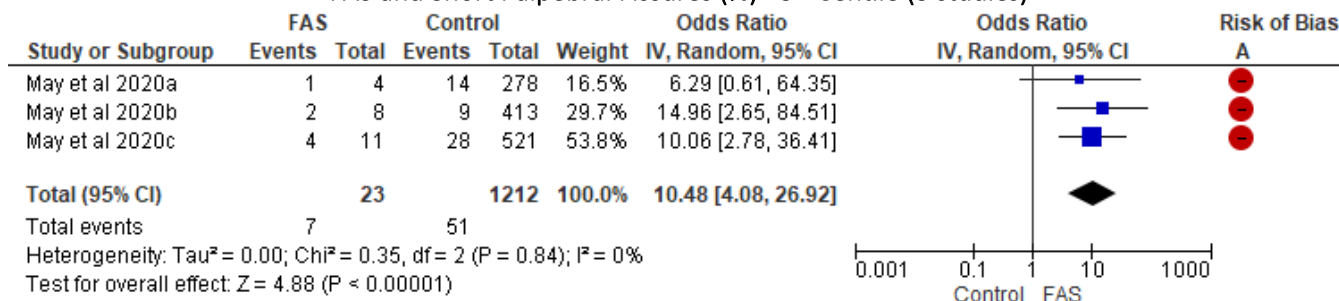
FASD and Short Palpebral Fissures (%) <3rd Centile (1 study)



Risk of bias legend

(A) Overall RoB

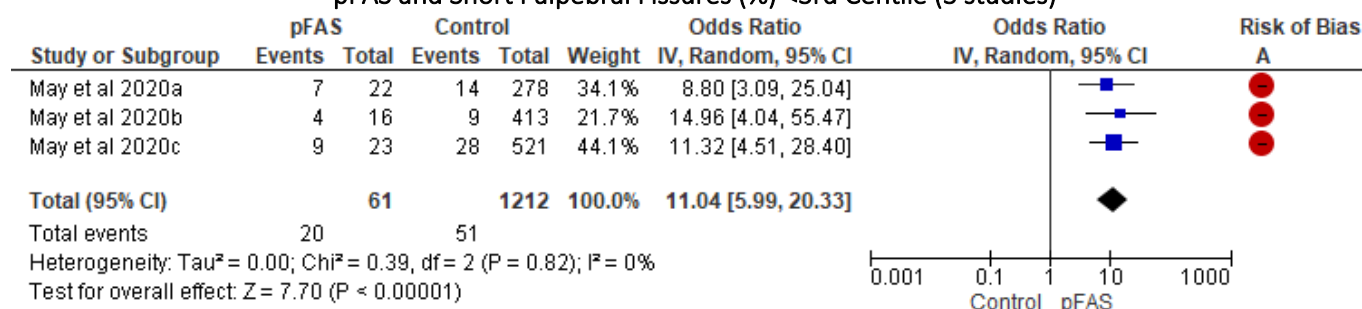
FAS and Short Palpebral Fissures (%) <3rd Centile (3 studies)



Risk of bias legend

(A) Overall RoB

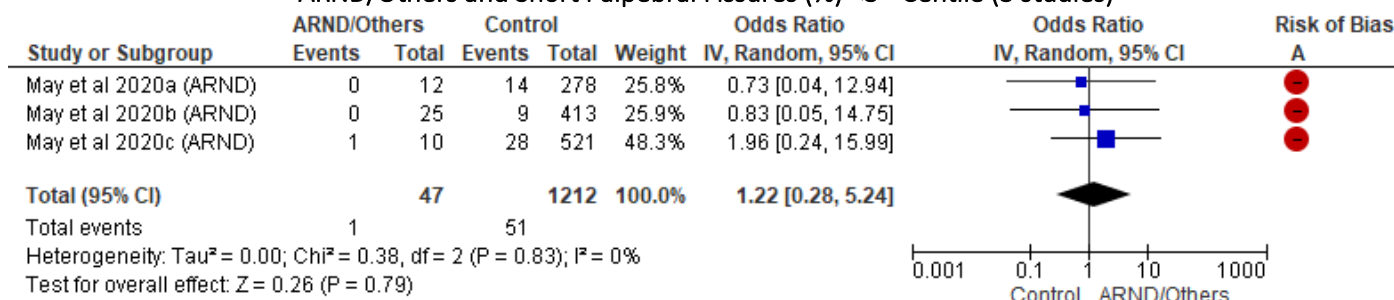
pFAS and Short Palpebral Fissures (%) <3rd Centile (3 studies)



Risk of bias legend

(A) Overall RoB

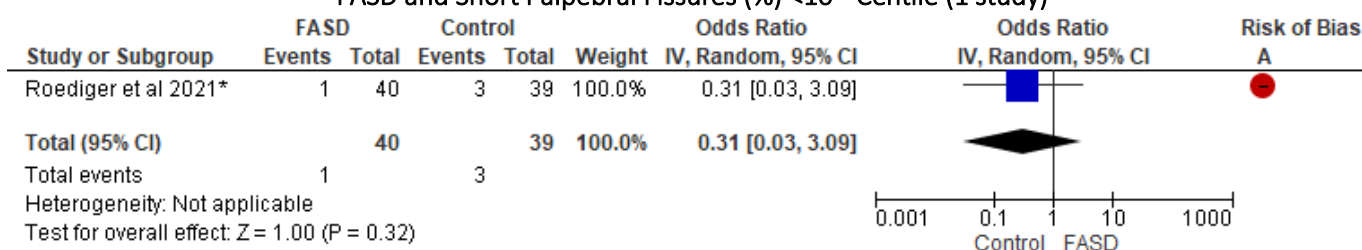
ARND/Others and Short Palpebral Fissures (%) <3rd Centile (3 studies)



Risk of bias legend

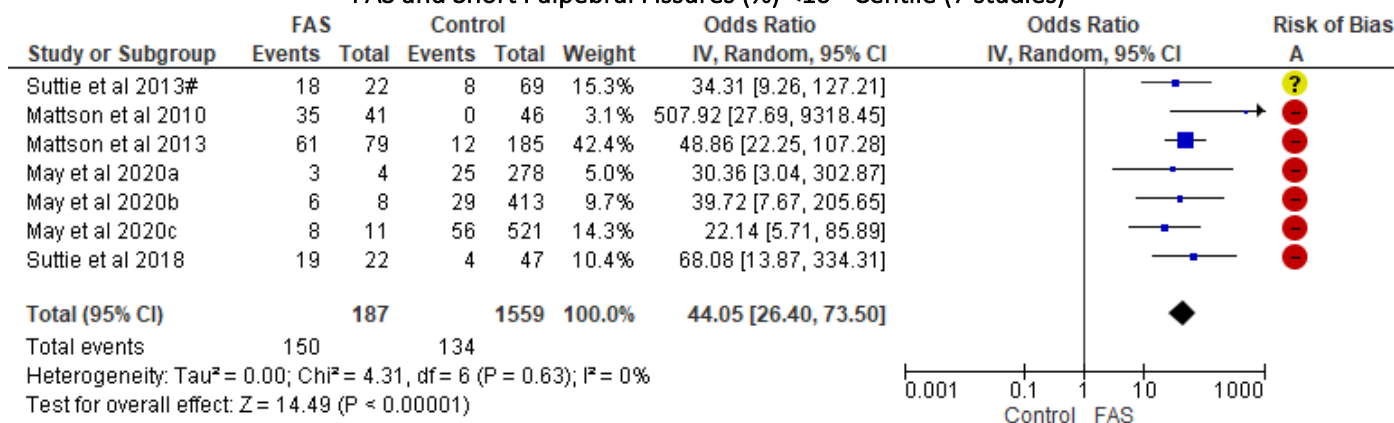
(A) Overall RoB

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 (%) <10th CentileFASD and Short Palpebral Fissures (%) <10th Centile (1 study)

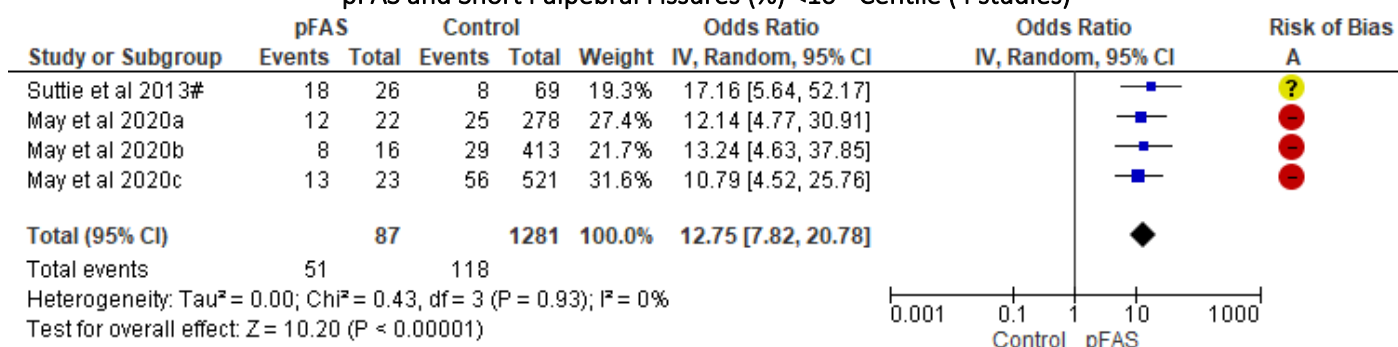
Risk of bias legend

(A) Overall RoB

FAS and Short Palpebral Fissures (%) <10th Centile (7 studies)

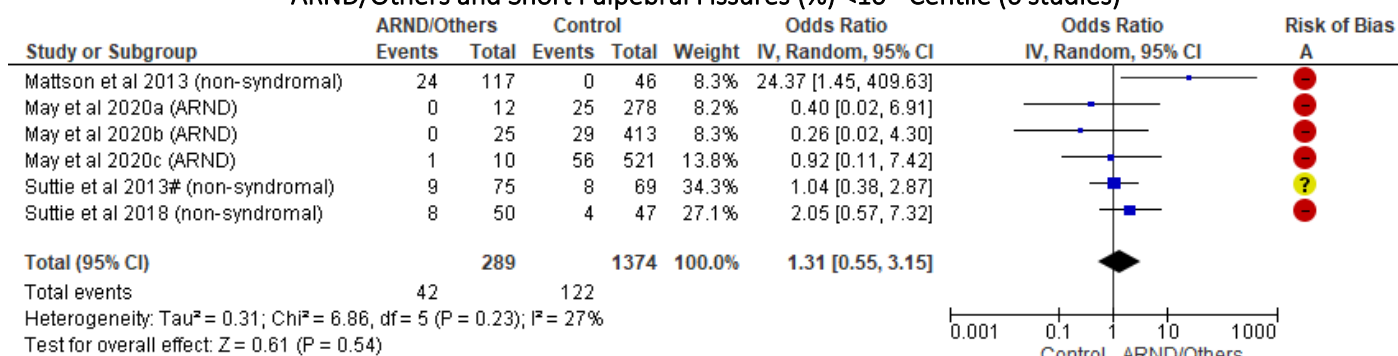
Risk of bias legend

(A) Overall RoB

pFAS and Short Palpebral Fissures (%) <10th Centile (4 studies)

Risk of bias legend

(A) Overall RoB

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

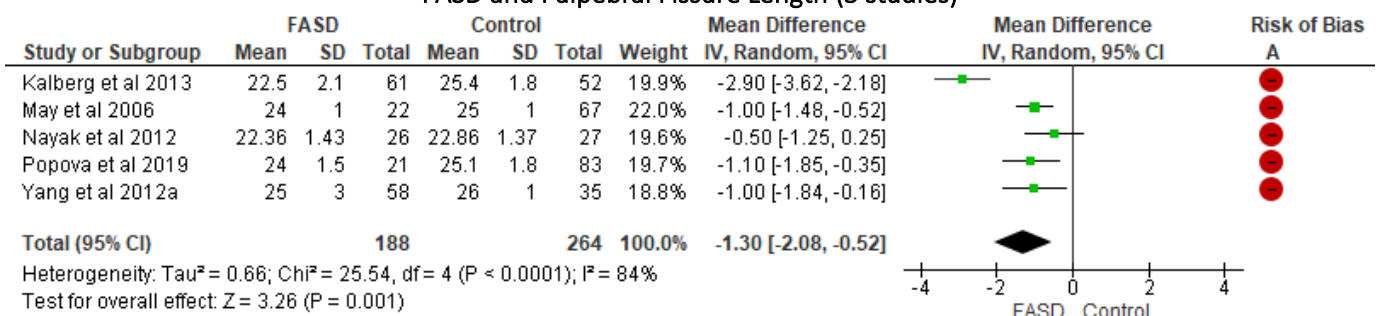
Risk of bias legend

(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)

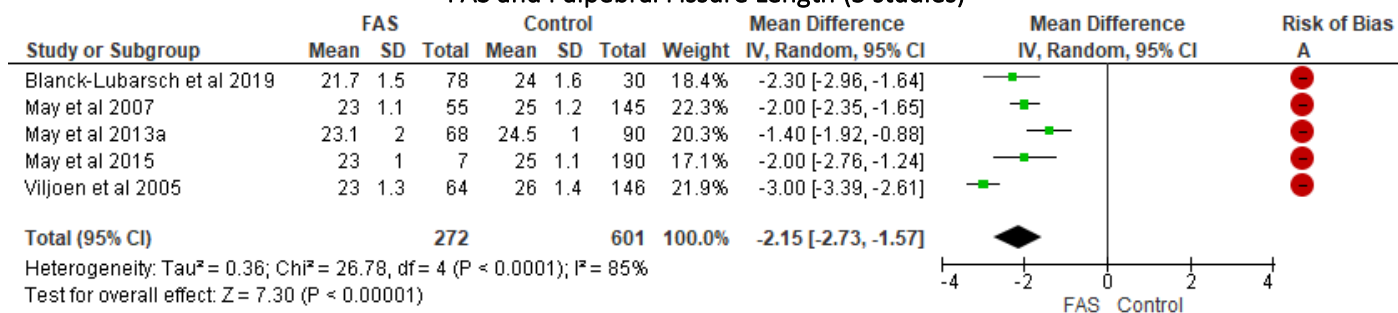
FASD and Palpebral Fissure Length (5 studies)



Risk of bias legend

(A) Overall RoB

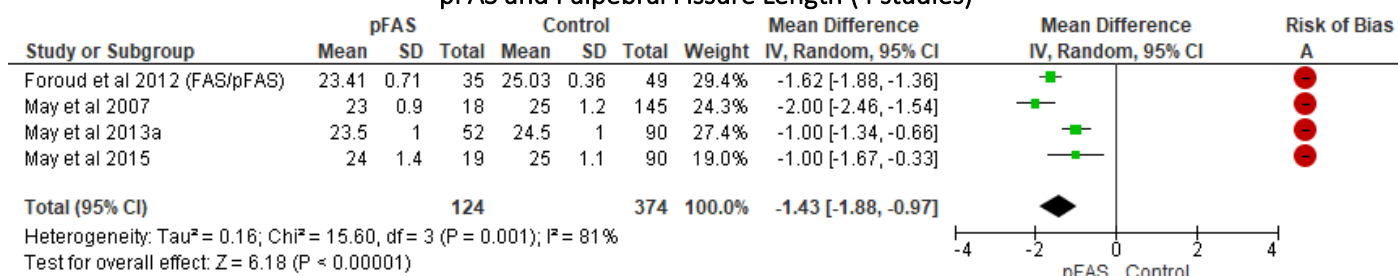
FAS and Palpebral Fissure Length (5 studies)



Risk of bias legend

(A) Overall RoB

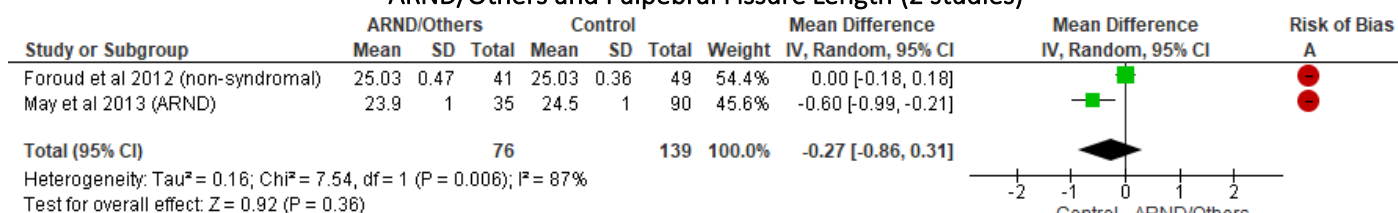
pFAS and Palpebral Fissure Length (4 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Palpebral Fissure Length (2 studies)



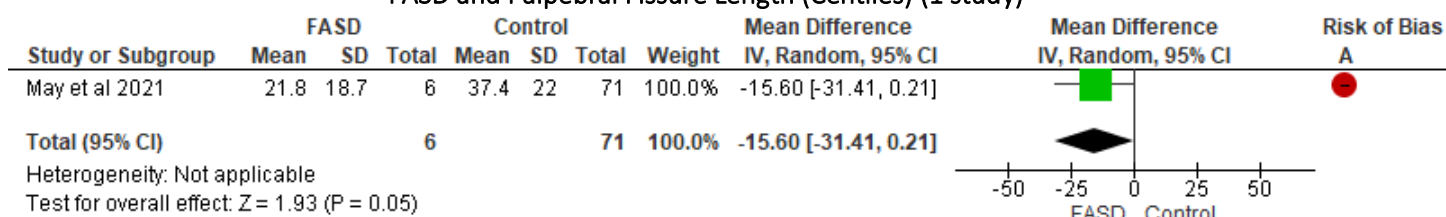
Risk of bias legend

(A) Overall RoB

Notes: Foroud 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)

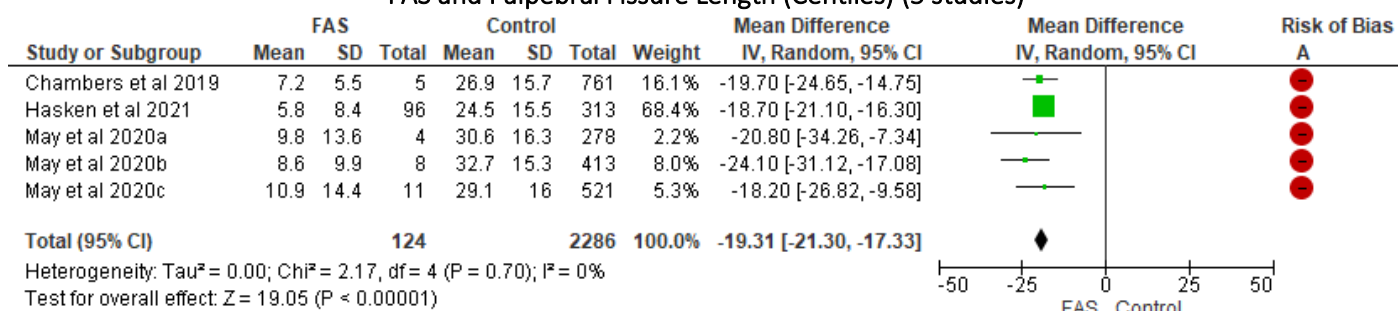
FASD and Palpebral Fissure Length (Centiles) (1 study)



Risk of bias legend

(A) Overall RoB

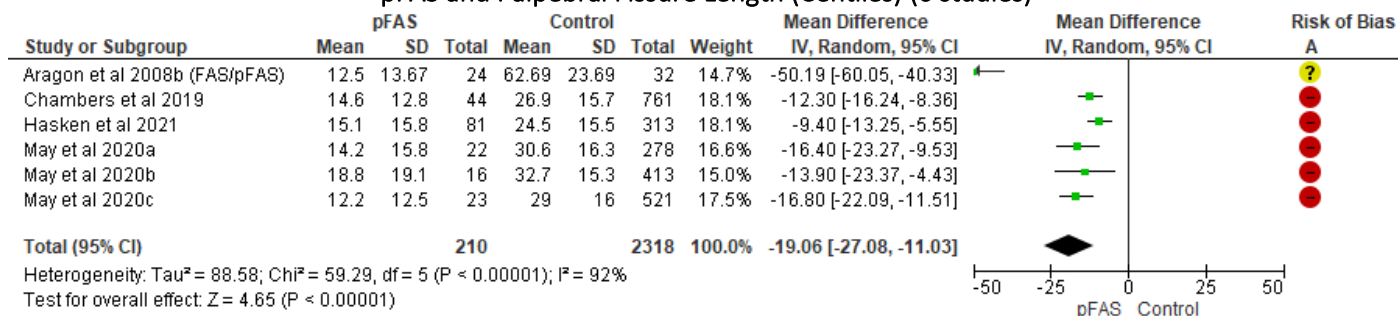
FAS and Palpebral Fissure Length (Centiles) (5 studies)



Risk of bias legend

(A) Overall RoB

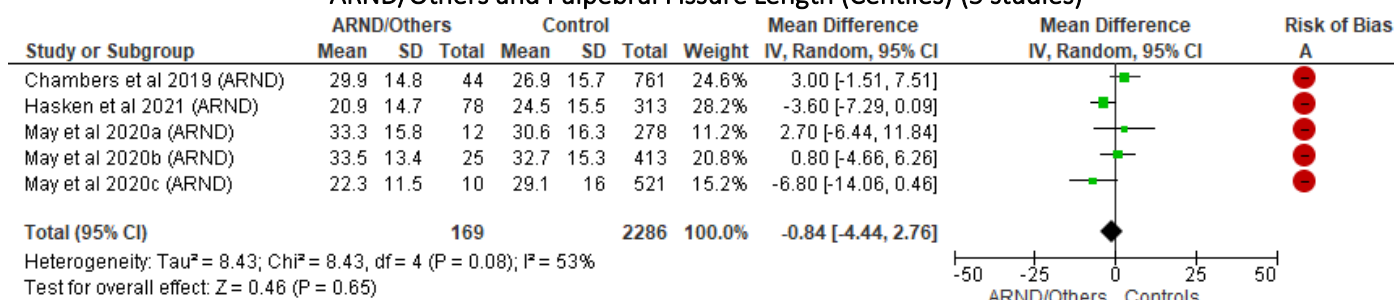
pFAS and Palpebral Fissure Length (Centiles) (6 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Palpebral Fissure Length (Centiles) (5 studies)

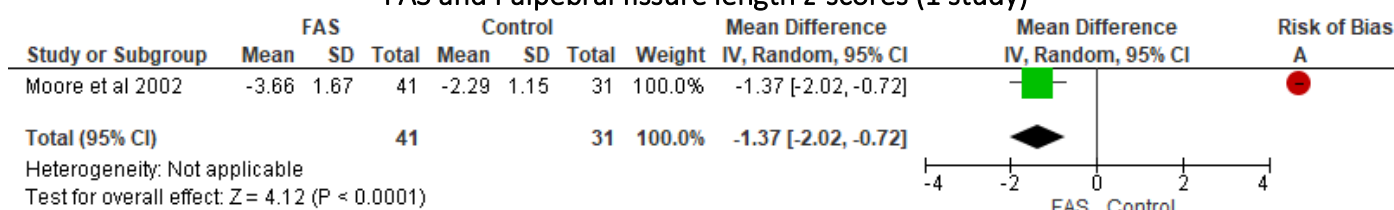
[Risk of bias legend](#)

(A) Overall RoB

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

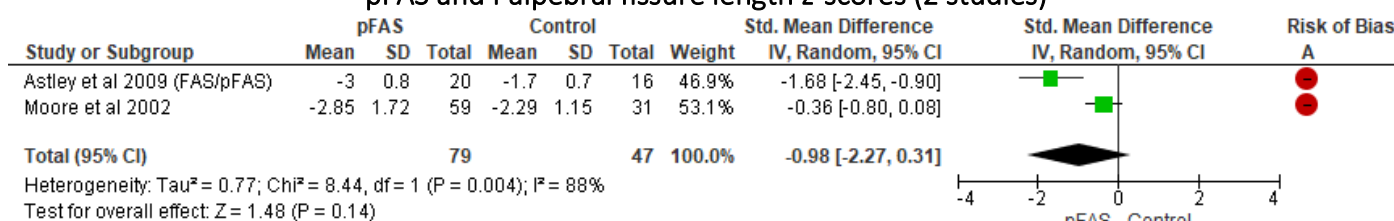
Palpebral Fissure Length (z-scores)

FAS and Palpebral fissure length z-scores (1 study)

[Risk of bias legend](#)

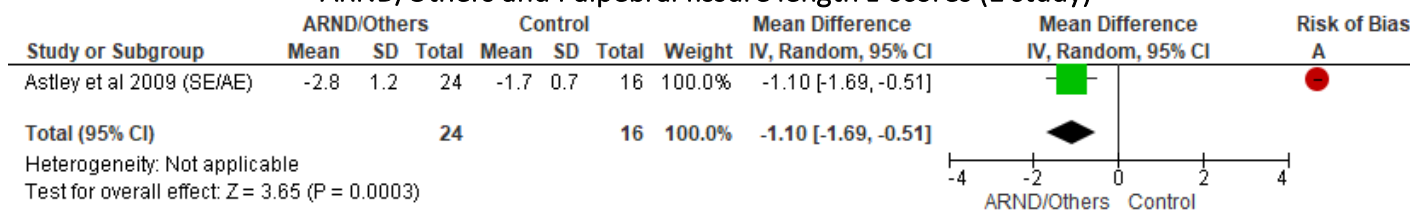
(A) Overall RoB

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

[Risk of bias legend](#)

(A) Overall RoB

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

[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.

Summary of available outcomes for other minor facial features

Other Minor Facial Features			
Study Type	Outcome	Data	# of studies
Exposure Studies	Strabismus	Strabismus (%)	2 studies: 1 moderate PAE, 1 very heavy PAE and 1 confirmed unquantified
	Interpupillary Distance	IPD (mm) (m/SD)	1 study: 1 heavy PAE
	Hypoplastic Midface	Hypoplastic Midface (%)	1 study: 1 moderate PAE, 1 very heavy PAE
	Ptosis	Ptosis (%)	2 studies: 1 moderate, 1 very heavy PAE and 1 confirmed unquantified
	Epicanthal Folds	Epicanthal Folds (%)	2 studies: 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 (%)	1 study: 1 moderate PAE, 1 very heavy PAE
	Anteverted Nares	Anteverted Nares (%)	2 studies: 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
Diagnosed Studies	Strabismus	Strabismus (%)	7x studies: 1x FASD, 5x FAS, 5x pFAS, 3x ARND/Others
	Interpupillary Distance	IPD (mm) (m/SD)	1 study: 1x FAS, 1x pFAS, and 1x ARND/Others
		Short IPD (%)	4 studies: 3x FAS, 3x pFAS and 1x ARND/Others
		IPD (centile)	6 studies: 2x FASD, 5x FAS, 5x pFAS, and 5x ARND/Others
	Hypoplastic Midface	Hypoplastic Midface (%)	7 studies: 1x FASD, 6x FAS, 5x pFAS, 3x ARND/Others
	Ptosis	Ptosis (%)	8x studies: 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 (%)	6 studies: 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)	5 studies: 2x FASD, 2x FAS, 2x pFAS (1x FAS/pFAS) and 2x ARND/Others
		Short ICD (%)	6 studies: 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 (%)	6 studies: 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)	5 studies 2x FASD, 4x FAS, 4x pFAS and 4x ARND/Others
	Mandibular Arc	Mandibular Arc (mm) (m/SD)	7 studies: 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

	Certainty assessment					No of patients		Effect		
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PAE	Control	Relative (95% CI)	Absolute (95% CI)	Certainty
EXPOSURE STUDIES										
STRABISMUS										
STRABISMUS (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	2/45	5/253	OR 2.31 (0.43 to 12.27)	-	⊕○○○ Very Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/19 (5.3%)	2/253 (2.0%)	OR 2.76 (0.31 to 24.86)	33 more per 1,000 (from 14 fewer to 314 more)	⊕○○○ Very Low
Confirmed Unquantifiable										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	5/12 (41.7%)	0/12 (0.0%)	OR 18.33 (0.88 to 380.70)	-	⊕○○○ Very Low
INTERPUPILLARY DISTANCE										
Interpupillary Distance (mm) (m/SD)										
Heavy PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	17	48	-	SMD 3.66 lower (4.51 lower to 2.81 lower)	⊕⊕○○ Low
HYPOPLASTIC MIDFACE										
Hypoplastic Midface (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	2/45	2/253	OR 5.84 (0.80 to 42.55)	-	⊕○○○ Very Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/19 (5.3%)	2/253 (0.8%)	OR 6.97 (0.60 to 80.61)	45 more per 1,000 (from 3 fewer to 383 more)	⊕○○○ Very Low
PTOSIS										
Ptosis (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/45	2/253	OR 2.85 (0.25 to 32.13)	-	⊕○○○ Very Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	0/19 (0.0%)	2/253 (0.8%)	OR 2.58 (0.12 to 55.63)	12 more per 1,000 (from 7 fewer to 299 more)	⊕○○○ Very Low
Confirmed Unquantifiable										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/12 (8.3%)	0/12 (0.0%)	OR 3.26 (0.12 to 88.35)	-	⊕○○○ Very Low
EPICANTHAL FOLDS										
Epicanthal Folds (%)										
Moderate PAE										

1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	25/45	144/253	OR 0.95 (0.50 to 1.79)	-	⊕○○○ Very Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	11/19 (57.9%)	144/253 (56.9%)	OR 1.04 (0.40 to 2.68)	10 more per 1,000 (from 223 fewer to 211 more)	⊕○○○ Very Low
Confirmed Unquantifiable										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/12 (8.3%)	1/12 (8.3%)	OR 1.00 (0.06 to 18.08)	-	⊕○○○ Very Low
NASAL BRIDGE (0 STUDIES)										
PROGNATHISM (0 STUDIES)										
INNERCANTHAL DISTANCE										
Innecanthal distance (mm) (m/SD)										
Heavy PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	17	48	-	SMD 1.42 lower (2.03 lower to 0.82 lower)	⊕⊕○○ Low
Short ICD (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	12/45	18/253	OR 4.75 (2.10 to 10.74)	-	⊕⊕○○ Low
Heavy PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	7/19 (36.8%)	18/253 (7.1%)	OR 7.62 (2.67 to 21.72)	297 more per 1,000 (from 99 more to 553 more)	⊕⊕○○ Low
ANTEVERTED NARES										
Anteverted Nares (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	8/45	45/253	OR 1.00 (0.44 to 2.29)	-	⊕○○○ Very Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	5/19 (26.3%)	8/45 (17.8%)	OR 1.65 (0.57 to 4.82)	85 more per 1,000 (from 87 fewer to 383 more)	⊕○○○ Very Low
Confirmed Unquantifiable										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	8/12 (66.7%)	0/12 (0.0%)	OR 47.22 (2.24 to 996.02)	-	⊕○○○ Very Low
OUTERCANTHAL DISTANCE										
Outercanthal distance (mm) (m/SD)										
Heavy PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	17	48	-	SMD 3.16 lower (3.95 lower to 2.37 lower)	⊕⊕○○ Low
MANDIBULAR ARC (0 STUDIES)										
MAXILLARY ARC (0 STUDIES)										
DIAGNOSED STUDIES										
STRABISMUS										
Strabismus (%)										
FASD										

5	serious _a	not serious	not serious	serious ^d	none	425	2216	-	SMD 0.24 lower (0.57 lower to 0.09 higher)	⊕⊕○○ Low
HYPOPLASTIC MIDFACE										
Hypoplastic Midface (%)										
FASD										
1	serious _a	not serious	not serious	very serious ^{d,e,f}	none	6/22 (27.3%)	8/67 (11.9%)	OR 2.77 (0.84 to 9.13)	-	⊕○○○ Very Low
FAS										
6	serious _a	serious ^b	not serious	serious ^e	none	220/346 (63.58%)	285/127 6 (22.34%)	OR 6.60 (3.64 to 11.96)		⊕○○○ Very Low
pFAS										
5	serious _a	not serious	serious ^c	not serious	none	125/212 (58.96%)	240/950 (25.26%)	OR 3.68 (2.51 to 5.39)		⊕⊕○○ Low
ARND/Others										
3	serious _a	not serious	serious ^c	serious ^{e,f}	none	50/100 (50.0%)	190/715 (26.6%)	OR 2.58 (1.58 to 4.22)	217 more per 1,000 (from 98 more to 339 more)	⊕○○○ Very Low
PTOSIS										
Ptosis (%)										
FASD										
1	serious _a	not serious	not serious	serious ^{e,f}	none	3/22 (13.6%)	0/67 (0.0%)	OR 24.23 (1.20 to 489.48)	-	⊕⊕○○ Low
FAS										
6	serious _a	not serious	serious ^c	serious ^{e,f}	none	52/329 (15.8%)	62/1659 (3.7%)	OR 7.34 (3.98 to 13.57)	-	⊕○○○ Very Low
pFAS										
6	serious _a	not serious	not serious	serious ^f	none	21/269 (7.8%)	68/1692 (4.01%)	OR 2.69 (1.53 to 4.71)	-	⊕⊕○○ Low
ARND/Others										
4	serious _a	not serious	not serious	very serious ^{d,e,f}	none	5/159 (3.1%)	59/1368 (4.3%)	OR 1.07 (0.43 to 2.69)	3 more per 1,000 (from 24 fewer to 65 more)	⊕○○○ Very Low
EPICANTHAL FOLDS										
Epicanthal Folds (%)										
FASD										
2	serious _a	not serious	not serious	serious ^{e,f}	none	18/48 (37.5%)	12/94 (12.8%)	OR 4.61 (1.86 to 11.41)	275 more per 1,000 (from 86 more to 498 more)	⊕⊕○○ Low
FAS										
4	serious _a	not serious	serious ^c	not serious	none	116/199 (58.29%)	179/543 (32.96%)	OR 2.34 (1.66 to 3.32)	-	⊕⊕○○ Low
pFAS										
3	serious _a	not serious	serious ^c	not serious	none	50/93 (53.76%)	134/397 (33.75%)	OR 2.12 (1.29 to 3.47)	-	⊕⊕○○ Low
ARND/Others										
2	serious _a	serious ^b	not serious	very serious ^{d,e,f}	none	29/48 (60.4%)	63/252 (25.0%)	OR 1.86 (0.13 to 27.8)	133 more per 1,000 (from 208)	⊕○○○ Very low

									fewer to 651 more)	
NASAL BRIDGE										
Flat Nasal Bridge (%)										
FASD										
1	serious _a	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	Not estimable	-	N/A
FAS										
4	serious _a	not serious	serious ^c	serious ^{e,f}	none	94/194 (85.9%)	87/571 (15.24%)	OR 3.70 (2.10 to 6.55)	-	⊕○○○ Very Low
pFAS										
4	serious _a	serious ^b	not serious	serious ^{e,f}	none	44/128 (34.38%)	81/604 (13.41%)	OR 3.51 (1.17 to 10.55)	-	⊕○○○ Very Low
ARND/Others										
1	serious _a	not serious	serious ^c	very serious ^{d,e,f}	none	20/35 (57.1%)	33/90 (36.7%)	OR 2.30 (1.04 to 5.10)	204 more per 1,000 (from 9 more to 380 more)	⊕○○○ Very Low
Nasal Bridge Length (mm) (m/SD)										
FAS/pFAS										
1	serious _a	not serious	serious ^c	serious ^{e,f}	none	35	49	-	SMD 3.29 lower (3.96 lower to 2.62 lower)	⊕○○○ Very Low
ARND/Others										
1	serious _a	not serious	serious ^c	serious ^{e,f}	none	41	49	-	SMD 1.69 lower (2.17 lower to 1.2 lower)	⊕○○○ Very Low
Nasal Bridge Length (z-score)										
FAS										
1	serious _a	not serious	not serious	serious ^{e,f}	none	39	31	-	SMD 0.75 lower (1.24 lower to 0.26 lower)	⊕⊕○○ Low
pFAS										
1	serious _a	not serious	not serious	very serious ^{d,e,f}	none	59	31	-	SMD 0.17 lower (0.61 lower to 0.26 higher)	⊕○○○ Very Low
PROGNATHISM										
Prognathism (%)										
FASD										
1	serious _a	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	Not estimable	-	N/A
FAS										
3	serious _a	not serious	serious ^c	serious ^{e,f}	none	12/187 (6.4%)	5/381 (1.3%)	OR 4.87 (1.75 to 13.61)	-	⊕○○○ Very Low
pFAS										
2	serious _a	not serious	serious ^c	very serious ^{d,e,f}	none	3/70 (4.2%)	5/253 (1.97%)	OR 2.12 (0.45 to 10.06)		⊕○○○ Very Low
ARND/Others										
1	serious _a	not serious	serious ^c	very serious ^{d,e,f}	none	1/35 (2.9%)	2/90 (2.2%)	OR 1.29 (0.11 to 14.74)	6 more per 1,000 (from 20 fewer to 229 more)	⊕○○○ Very Low
INNERCANTHAL DISTANCE										

Innercanthal distance (mm) (m/SD)										
FASD										
2	serious _a	not serious	not serious	very serious ^{d,e,f}	none	47	110	-	MD 0.45 higher (0.41 lower to 1.30 higher)	⊕○○○ Very Low
FAS										
2	serious _a	not serious	not serious	serious ^{e,f}	none	96	120	-	MD 1.64 lower (2.71 lower to 0.56 lower)	⊕⊕○○ Low
pFAS										
2	serious _a	not serious	serious ^c	serious ^{e,f}	none	87	139	-	MD 0.47 lower (0.73 lower to 0.22 lower)	⊕○○○ Very Low
ARND/Others										
2	serious _a	serious ^b	serious ^c	very serious ^{d,e,f}	none	76	139	-	MD 0.69 lower (2.68 lower to 1.3 higher)	⊕○○○ Very Low
Short innercanthal distance (%)										
FASD										
2	serious _a	not serious	not serious	very serious ^{d,e,f}	none	14/43 (32.6%)	43/150 (28.7%)	OR 1.48 (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 ^c	serious ^f	none	44/185 (23.78%)	43/381 (11.29%)	OR 2.33 (1.43 to 3.81)	-	⊕○○○ Very Low
pFAS										
3	serious _a	not serious	serious ^c	serious ^{d,f}	none	19/109 (17.43%)	61/414 (14.73%)	OR 1.19 (0.48 to 2.94)	-	⊕○○○ Very Low
ARND/Others										
1	serious _a	not serious	serious ^c	very serious ^{d,e,f}	none	9/38 (23.7%)	18/90 (20.0%)	OR 1.24 (0.50 to 3.08)	37 more per 1,000 (from 89 fewer to 235 more)	⊕○○○ Very Low
Innercanthal distance (centile)										
FAS										
2	serious _a	serious ^b	not serious	serious ^e	none	592	766	-	SMD 0.76 lower (1.37 lower to 0.15 lower)	⊕○○○ Very Low
pFAS										
2	serious _a	not serious	not serious	serious ^{d,e}	none	502	766	-	SMD 0.26 lower (0.54 lower to 0.02 higher)	⊕⊕○○ Low
ARND/Others										
2	serious _a	not serious	not serious	not serious	none	345	766	-	SMD 0.51 lower (0.64 lower to 0.37 lower)	⊕⊕⊕○ Moderate
Innercanthal Distance (z-score)										
FAS										
1	serious _a	not serious	not serious	very serious ^{d,e,f}	none	41	31	-	SMD 0.17 lower (0.76 lower to 0.41 higher)	⊕○○○ Very Low
pFAS										
1	serious _a	not serious	not serious	very serious ^{d,e,f}	none	59	31	-	SMD 0.12 higher (0.45 lower to 0.70 higher)	⊕○○○ Very Low

ANTEVERTED NARES										
Anteverted Nares (%)										
FASD										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	8/22 (36.4%)	6/67 (9.0%)	OR 5.81 (1.74 to 19.43)	-	⊕⊕○○ Low
FAS										
4	serious ^a	not serious	serious ^c	serious ^f	none	78/316	64/485	OR 1.92 (1.07 to 3.44)	-	⊕○○○ Very Low
pFAS										
4	serious ^a	not serious	serious ^c	serious ^f	none	61/209	84/518	OR 2.16 (1.16 to 4.02)	-	⊕○○○ Very Low
ARND/Others										
2	serious ^a	not serious	serious ^c	serious ^{d,f}	none	13/90 (14.4%)	47/194 (24.2%)	OR 0.51 (0.15 to 1.76)	-	⊕○○○ Very Low
OUTERCANTHAL DISTANCE										
Outer canthal distance (mm) (m/SD)										
FAS/pFAS										
1	serious ^a	not serious	serious ^c	very serious ^{d,e,f}	none	35	49	-	SMD 3.98 lower (4.74 lower to 3.23 lower)	⊕○○○ Very Low
ARND/Others										
1	serious ^a	not serious	serious ^c	serious ^{d,f}	none	41	49	-	SMD 3.88 higher (3.17 higher to 4.59 higher)	⊕○○○ Very Low
Outer canthal distance (centile)										
FASD										
2	serious ^a	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 ^b	not serious	serious ^e	none	355	1800	-	SMD 0.6 lower (0.87 lower to 0.33 lower)	⊕○○○ Very Low
ARND/Others										
4	serious ^a	serious ^b	not serious	serious ^{d,e}	none	289	1800	-	SMD 0.2 lower (0.61 lower to 0.21 higher)	⊕⊕○○ Low
MANDIBULAR ARC										
Mandibular Arc (mm) (m/SD)										
FASD										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	6	71	-	SMD 0.8 lower (1.64 lower to 0.05 higher)	⊕○○○ Very Low
FAS										
6	serious ^a	not serious	not serious	serious ^e	none	225	2167	-	SMD 1.24 lower (1.59 lower to 0.88 lower)	⊕⊕○○ 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/Others										
6	serious ^a	serious ^b	not serious	serious ^{d,e}	none	181	2167	-	SMD 0.23 lower (0.63 lower to 0.16 higher)	⊕○○○ Very Low
Mandibular Arc (z-score)										
FAS										
1	serious ^a	not serious	not serious	serious ^{e,f}	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 ^{d,e,f}	none	59	31	-	SMD 0.44 lower (1.04 lower to 0.16 higher)	⊕○○○ Very Low
MAXILLARY ARC										
Maxillary Arc (mm) (m/SD)										
FASD										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	6	71	-	SMD 0.7 lower (1.54 lower to 0.14 higher)	⊕○○○ Very Low
FAS										
6	serious ^a	not serious	not serious	serious ^e	none	225	2167	-	SMD 0.94 lower (1.35 lower to 0.54 lower)	⊕⊕○○ Low
pFAS										
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/Others										
6	serious ^a	serious ^b	not serious	very serious ^{d,e,f}	none	181	2167	-	SMD 0.15 lower (0.47 lower to 0.18 higher)	⊕○○○ Very Low
Maxillary Arc (z-score)										
FAS										
1	serious ^a	not serious	not serious	serious ^{e,f}	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 ^{d,e,f}	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.

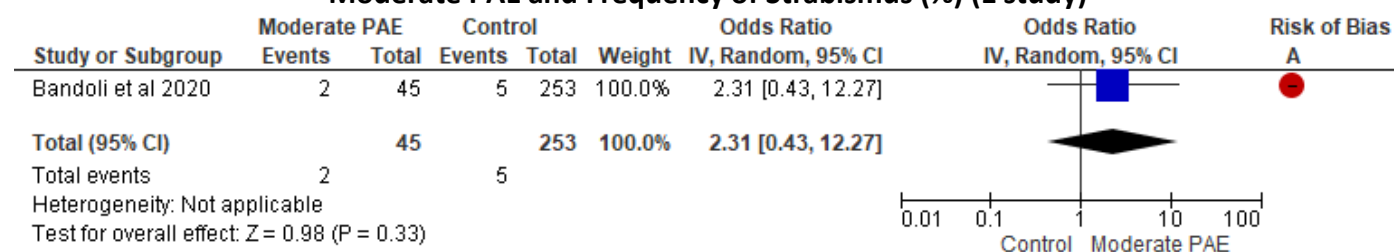
Meta-analyses for other minor facial features

Exposure studies

STRABISMUS

Frequency of Strabismus (%)

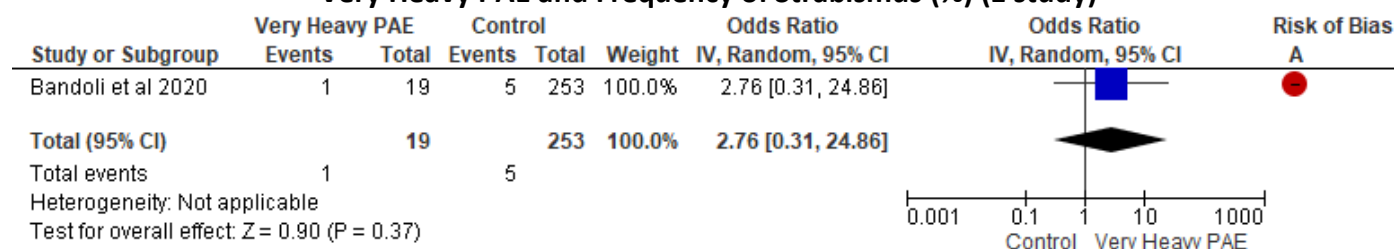
Moderate PAE and Frequency of Strabismus (%) (1 study)



Risk of bias legend

(A) Overall RoB

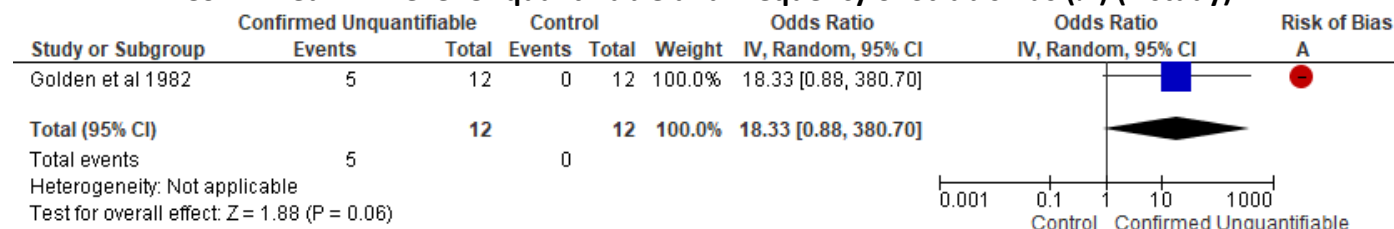
Very Heavy PAE and Frequency of Strabismus (%) (1 study)



Risk of bias legend

(A) Overall RoB

Confirmed PAE Level Unquantifiable and Frequency of Strabismus (%) (1 study)



Risk of bias legend

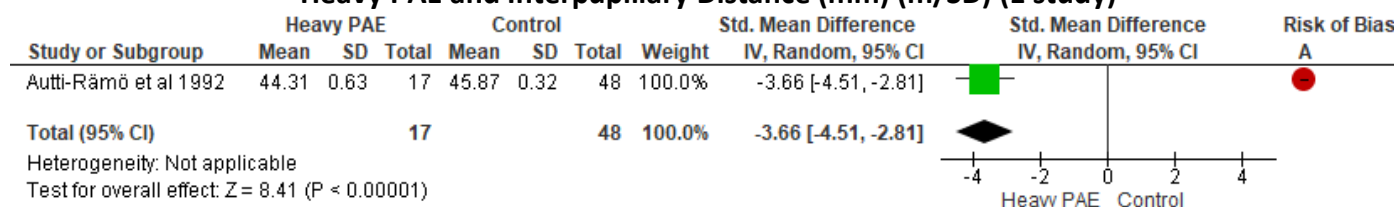
(A) Overall RoB

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

INTERPUPILLARY DISTANCE

Interpupillary Distance (mm) (m/SD)

Heavy PAE and Interpupillary Distance (mm) (m/SD) (1 study)



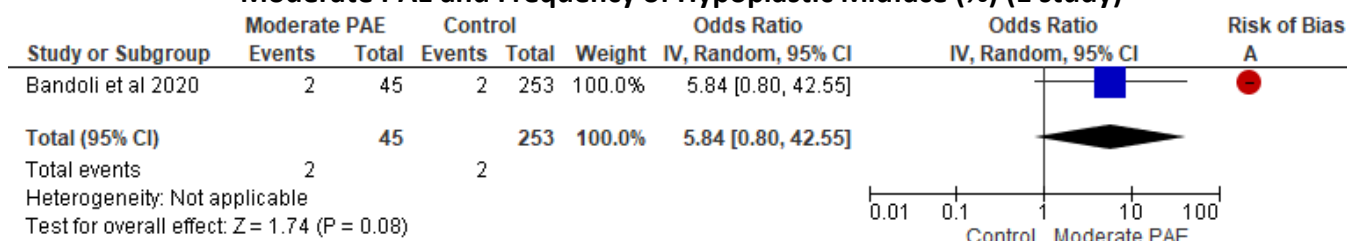
Risk of bias legend

(A) Overall RoB

HYPOPLASTIC MIDFACE

Hypoplastic Midface (%)

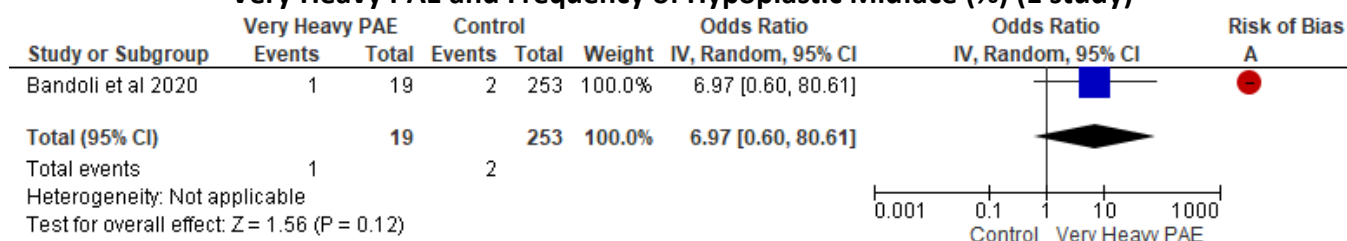
Moderate PAE and Frequency of Hypoplastic Midface (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

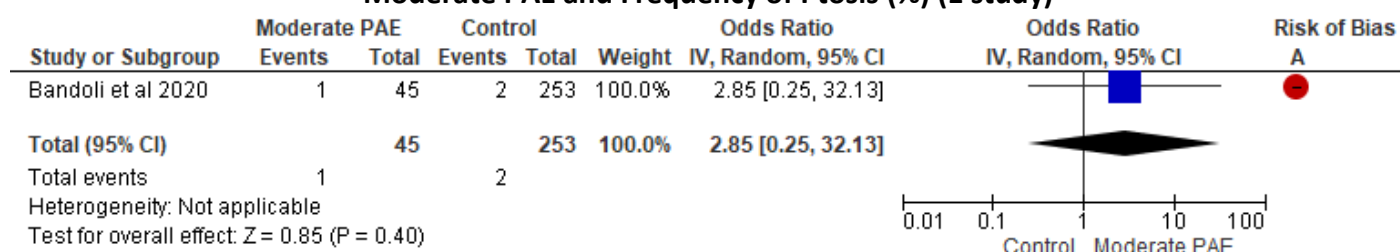
(A) Overall RoB

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 (%)

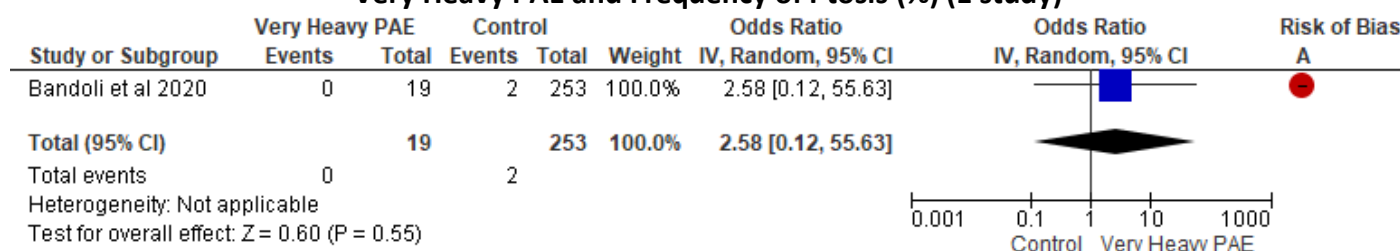
Moderate PAE and Frequency of Ptosis (%) (1 study)



Risk of bias legend

(A) Overall RoB

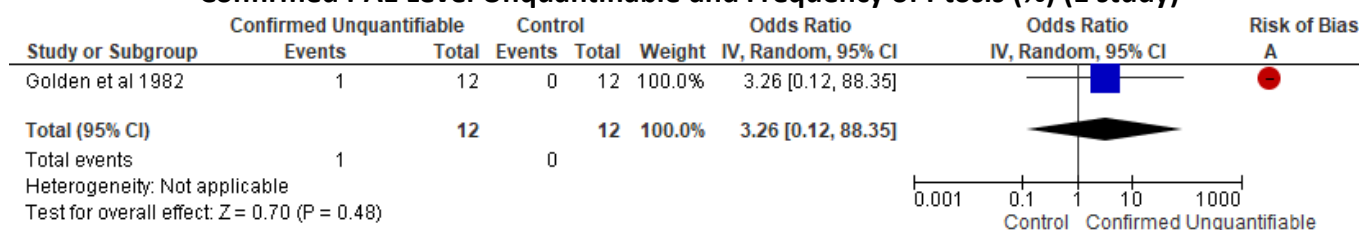
Very Heavy PAE and Frequency of Ptosis (%) (1 study)



Risk of bias legend

(A) Overall RoB

Confirmed PAE Level Unquantifiable and Frequency of Ptosis (%) (1 study)



[Risk of bias legend](#)

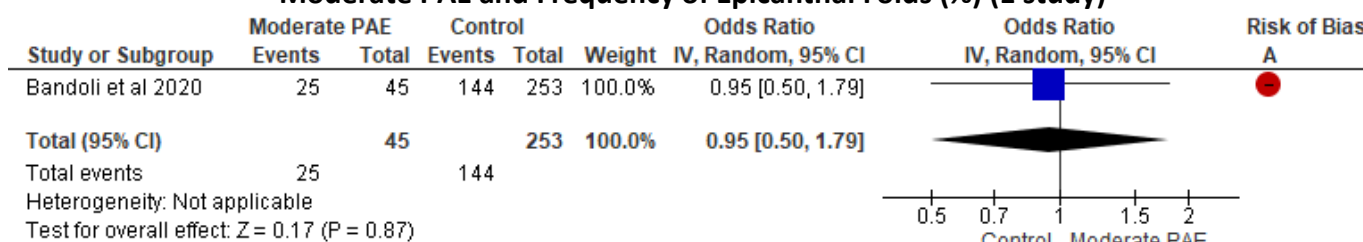
(A) Overall RoB

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

EPICANTHAL FOLDS

Epicanthal Folds (%)

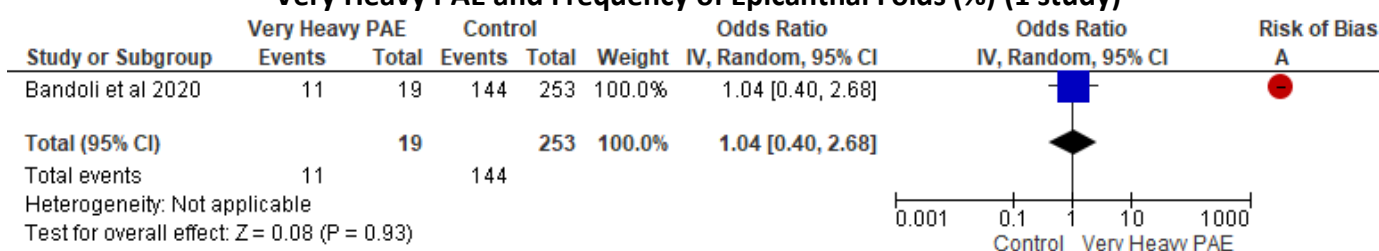
Moderate PAE and Frequency of Epicanthal Folds (%) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

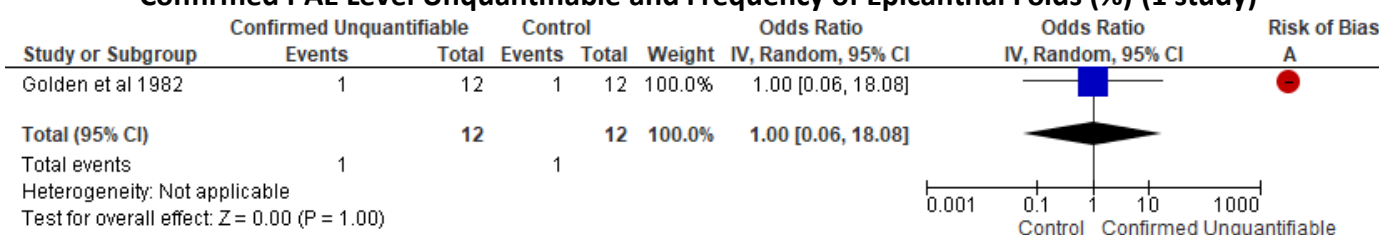
Very Heavy PAE and Frequency of Epicanthal Folds (%) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

Confirmed PAE Level Unquantifiable and Frequency of Epicanthal Folds (%) (1 study)



[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.

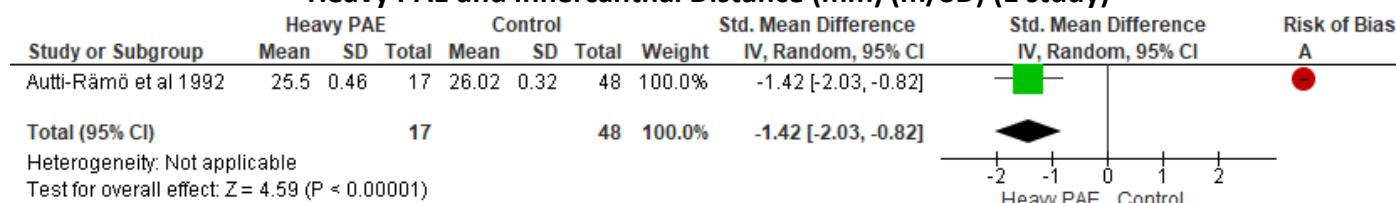
NASAL BRIDGE (0 STUDIES)

PROGNATHISM (0 STUDIES)

INNERCANTHAL DISTANCE

Innercanthal distance (mm) (m/SD)

Heavy PAE and Innercanthal Distance (mm) (m/SD) (1 study)

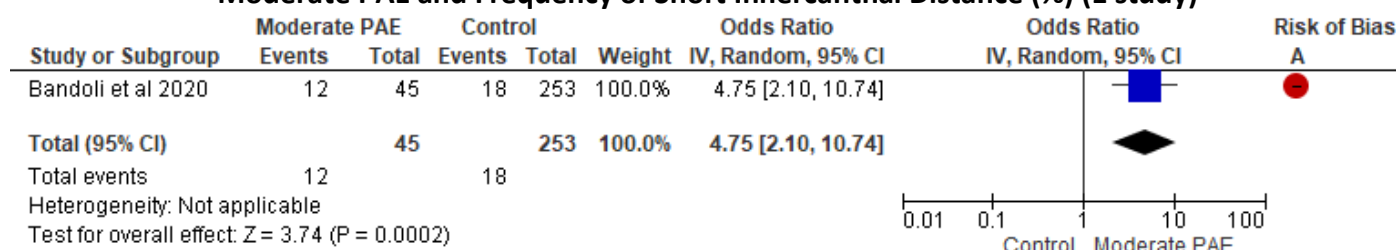


[Risk of bias legend](#)

(A) Overall RoB

Short Innercanthal distance (%)

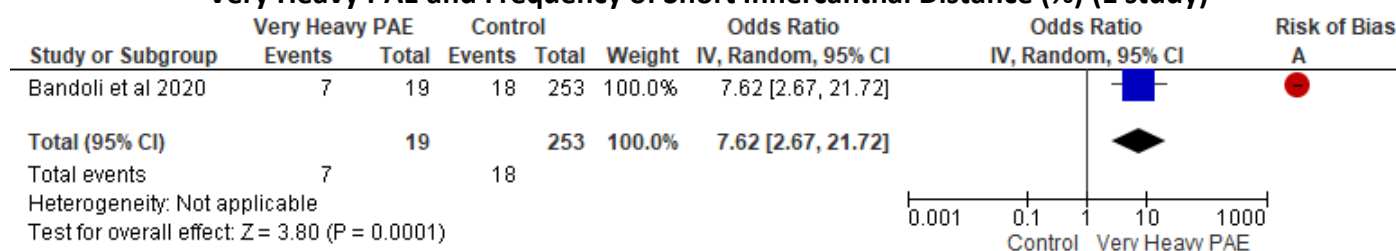
Moderate PAE and Frequency of Short Innercanthal Distance (%) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

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



[Risk of bias legend](#)

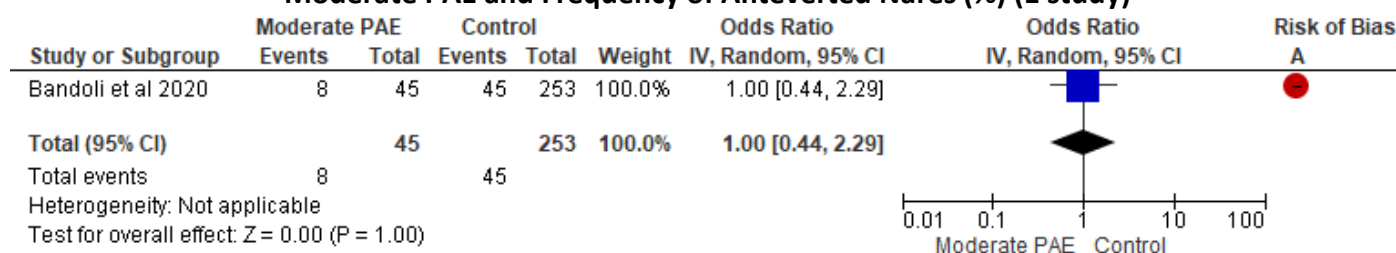
(A) Overall RoB

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

Anteverted Nares (%)

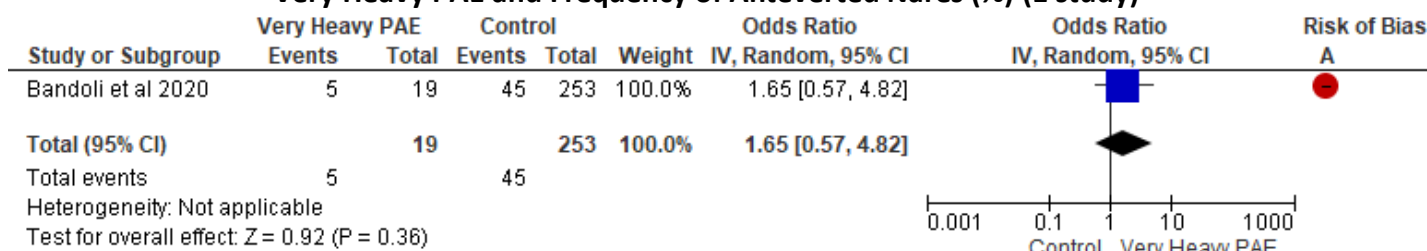
Moderate PAE and Frequency of Anteverted Nares (%) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

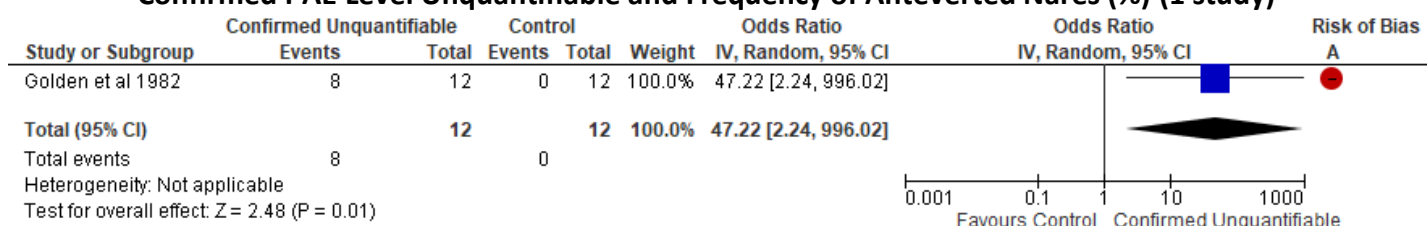
Very Heavy PAE and Frequency of Anteverted Nares (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

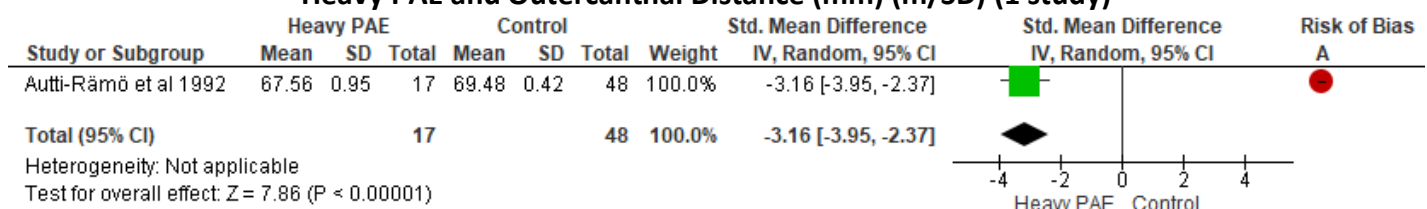
(A) Overall RoB

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

Outer canthal distance (mm) (m/SD)

Heavy PAE and Outer canthal distance (mm) (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

MANDIBULAR ARC (0 STUDIES)

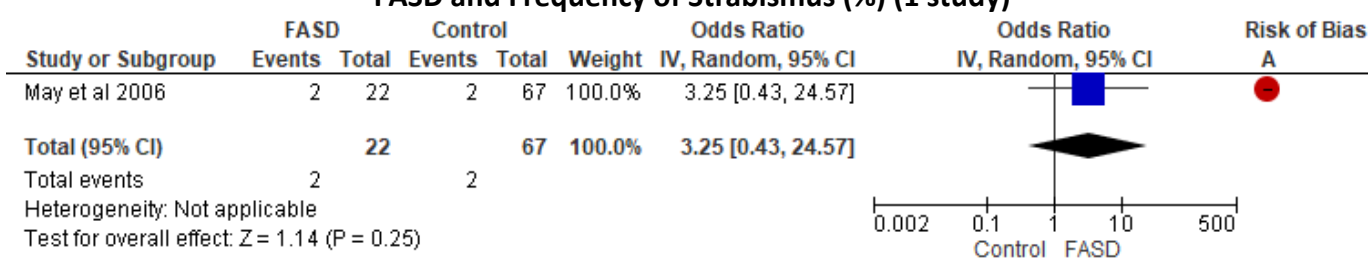
MAXILLARY ARC (0 STUDIES)

Diagnosed studies

STRABISMUS

Strabismus (%)

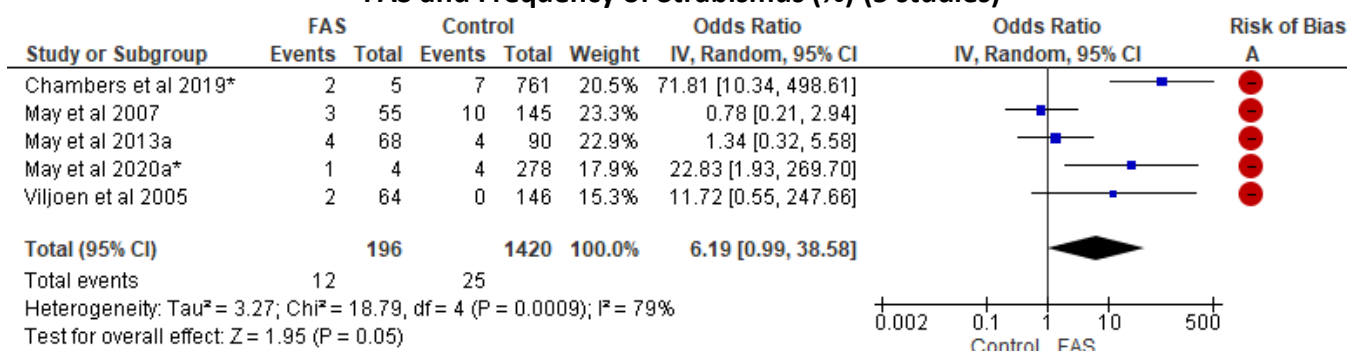
FASD and Frequency of Strabismus (%) (1 study)



Risk of bias legend

(A) Overall RoB

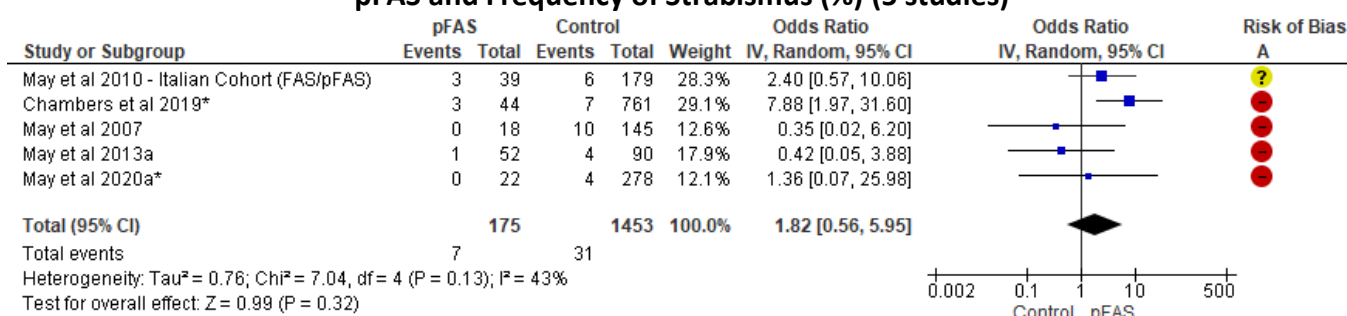
FAS and Frequency of Strabismus (%) (5 studies)



Risk of bias legend

(A) Overall RoB

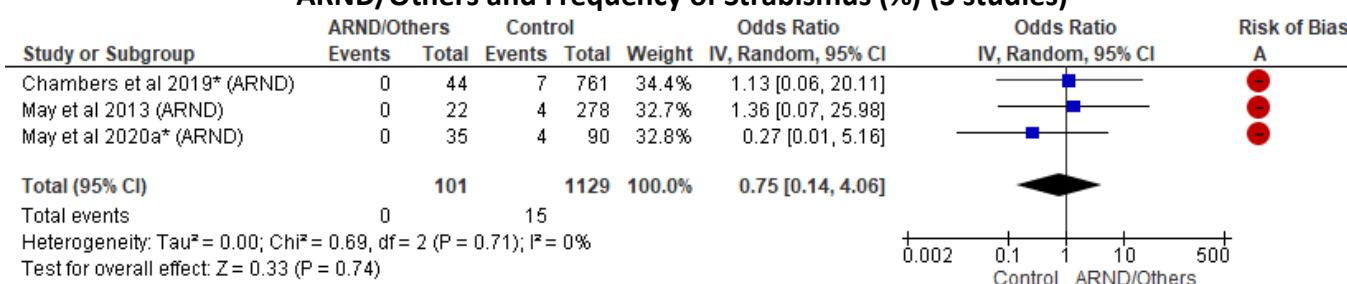
pFAS and Frequency of Strabismus (%) (5 studies)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

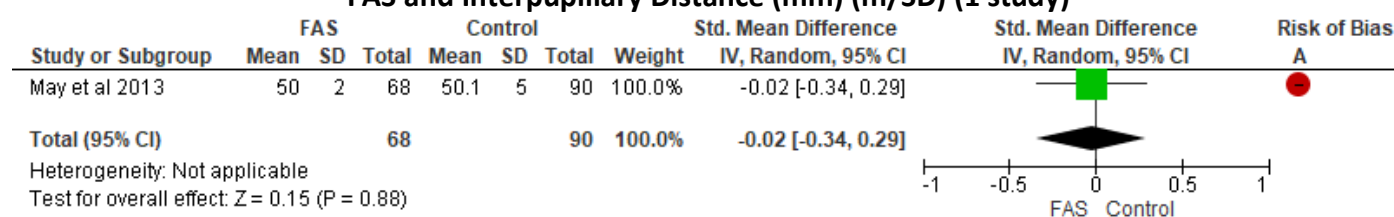
(A) Overall RoB

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

INTERPUPILLARY DISTANCE

Interpupillary Distance (mm) (m/SD)

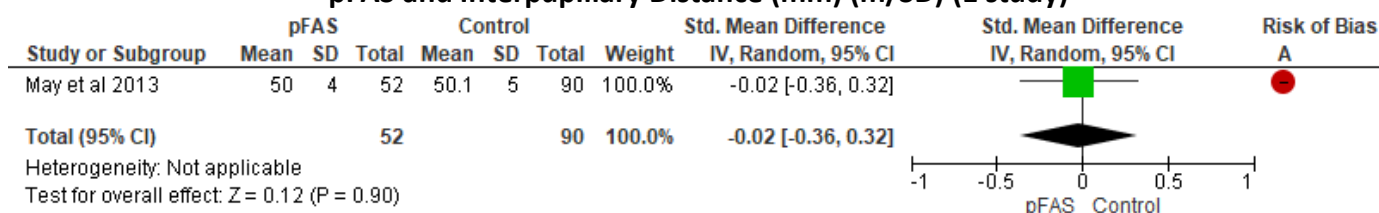
FAS and Interpupillary Distance (mm) (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

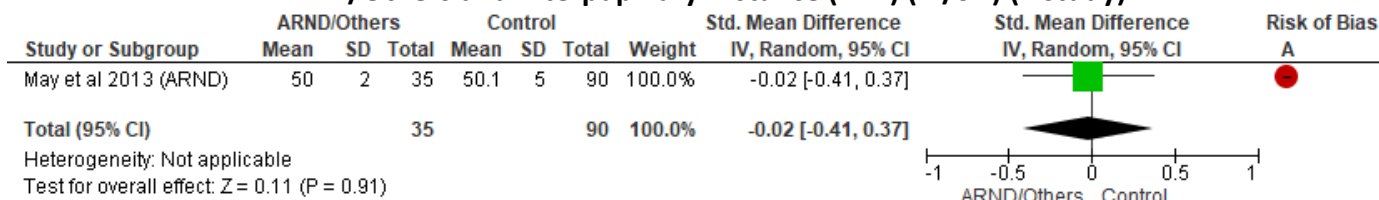
pFAS and Interpupillary Distance (mm) (m/SD) (1 study)



[Risk of bias legend](#)

(A) Overall RoB

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

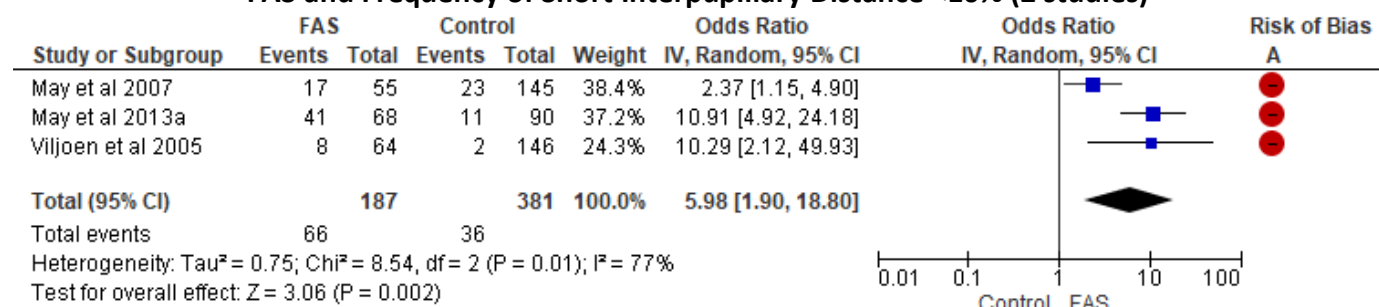


[Risk of bias legend](#)

(A) Overall RoB

Frequency Short Inter Pupillary Distance <10%

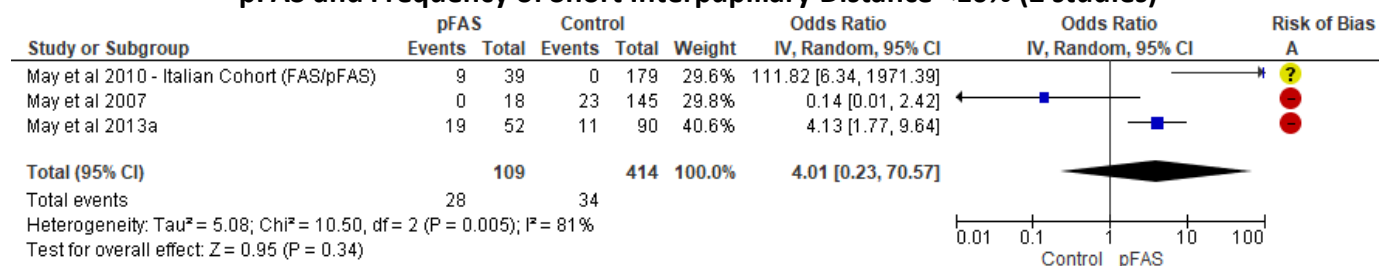
FAS and Frequency of Short Interpupillary Distance <10% (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

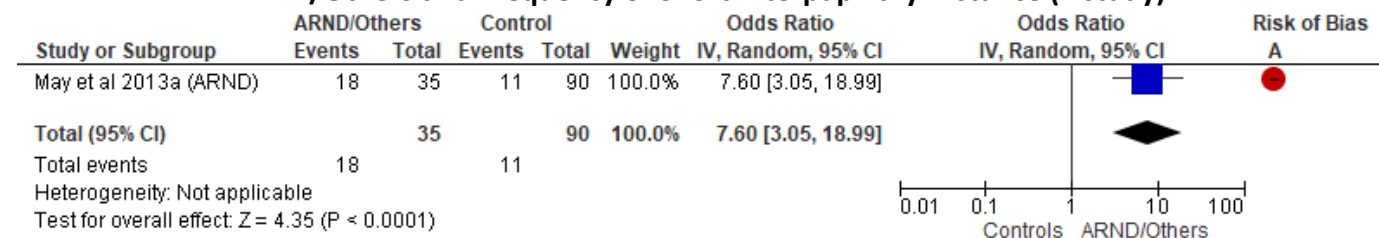
pFAS and Frequency of Short Interpupillary Distance <10% (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and Frequency of Short Interpupillary Distance (1 study)

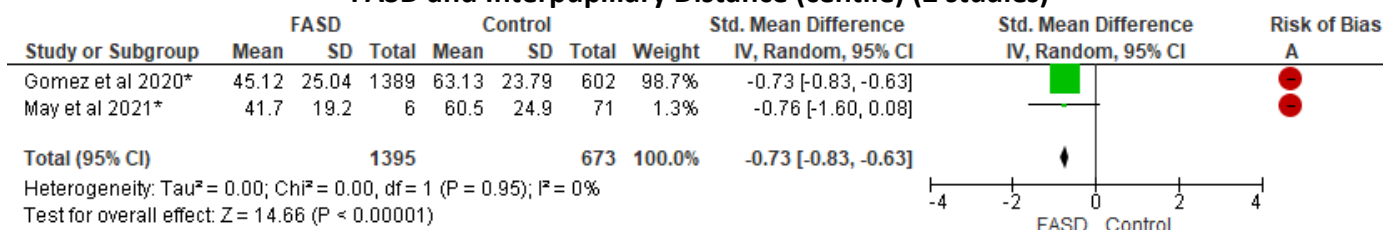


[Risk of bias legend](#)

(A) Overall RoB

Interpupillary Distance (centile)

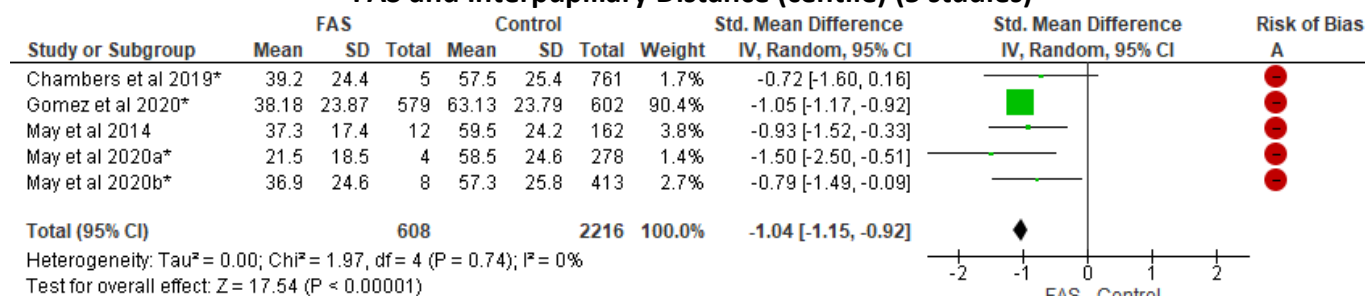
FASD and Interpupillary Distance (centile) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

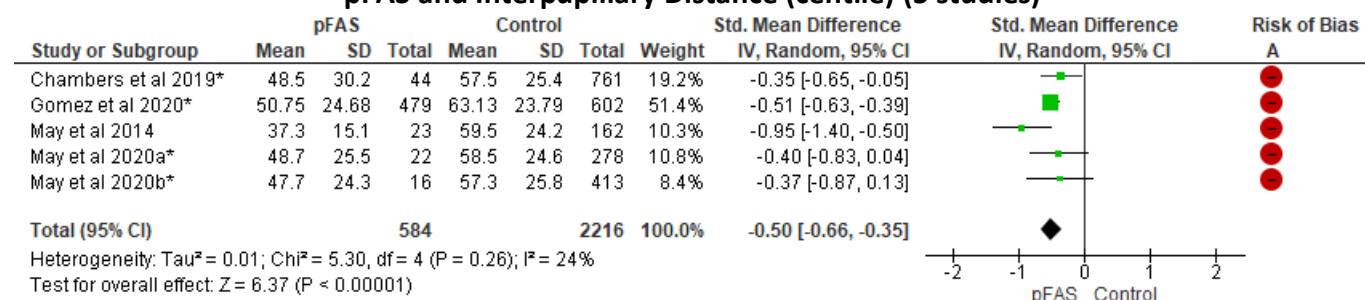
FAS and Interpupillary Distance (centile) (5 studies)



[Risk of bias legend](#)

(A) Overall RoB

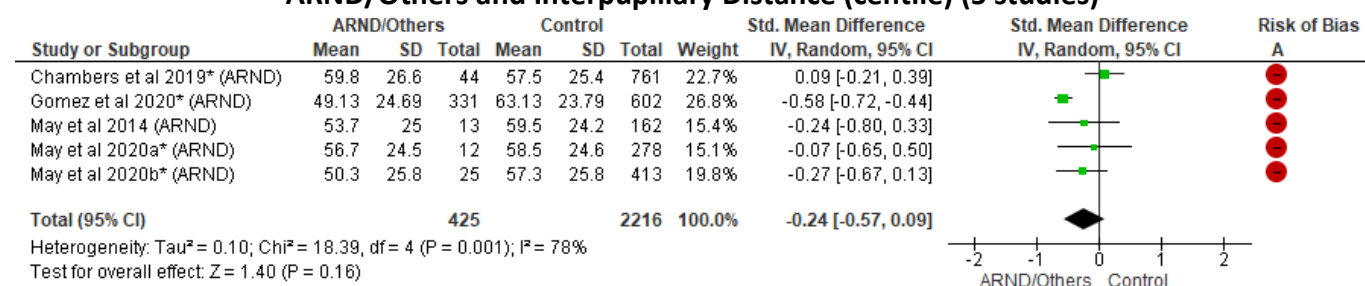
pFAS and Interpupillary Distance (centile) (5 studies)



[Risk of bias legend](#)

(A) Overall RoB

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



[Risk of bias legend](#)

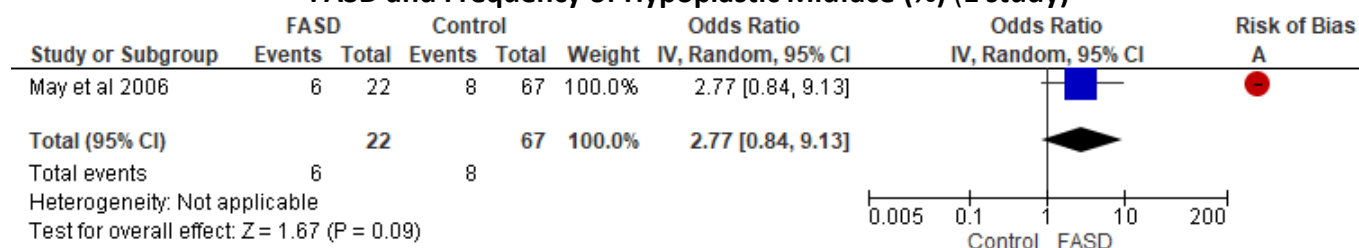
(A) Overall RoB

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

HYPOPLASTIC MIDFACE

Hypoplastic Midface (%)

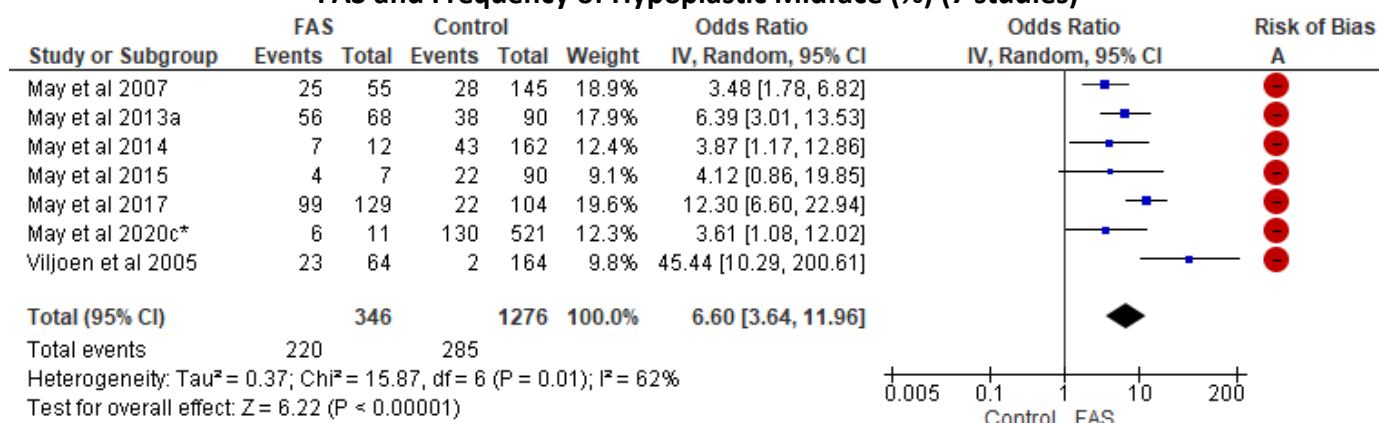
FASD and Frequency of Hypoplastic Midface (%) (1 study)



Risk of bias legend

(A) Overall RoB

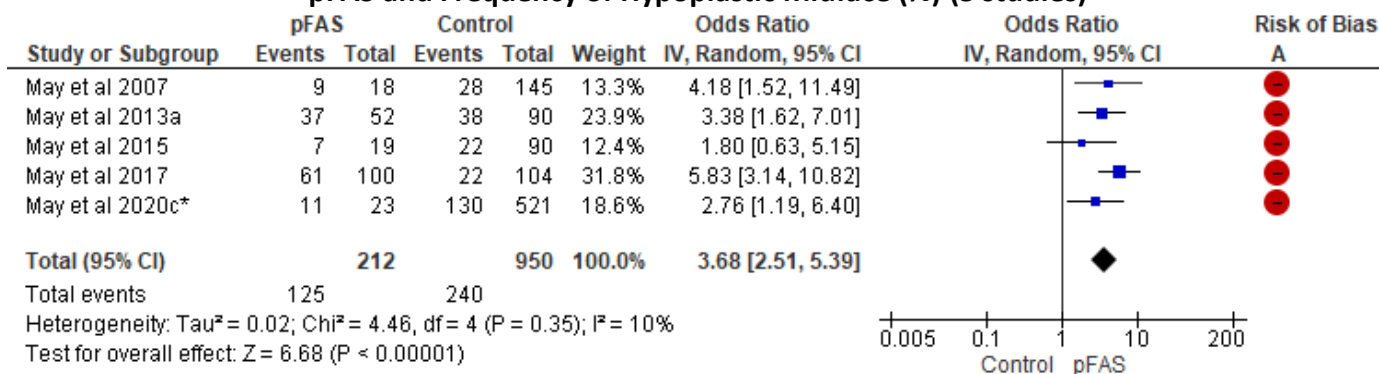
FAS and Frequency of Hypoplastic Midface (%) (7 studies)



Risk of bias legend

(A) Overall RoB

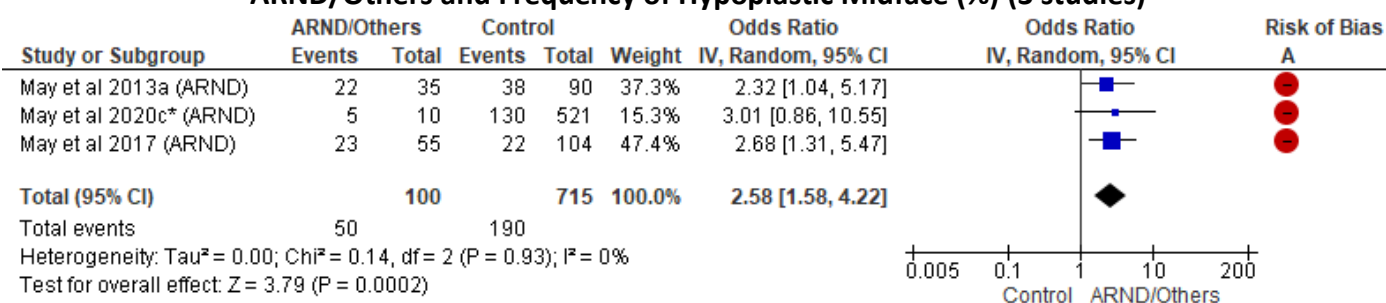
pFAS and Frequency of Hypoplastic Midface (%) (5 studies)



Risk of bias legend

(A) Overall RoB

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



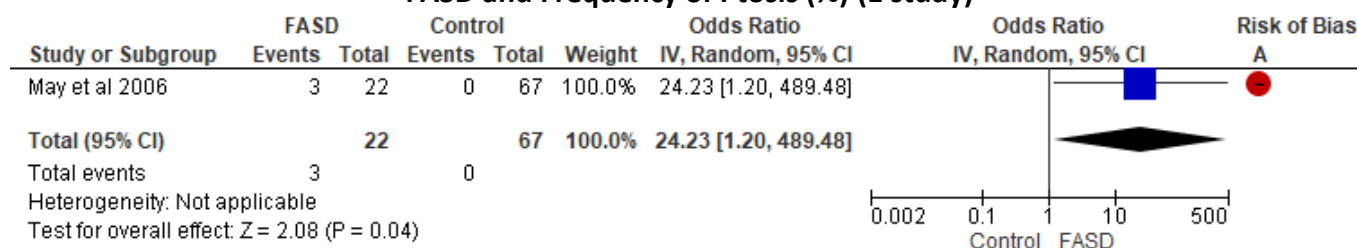
Risk of bias legend

(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 reports ARND and non-syndromal, used former.

Ptosis (%)

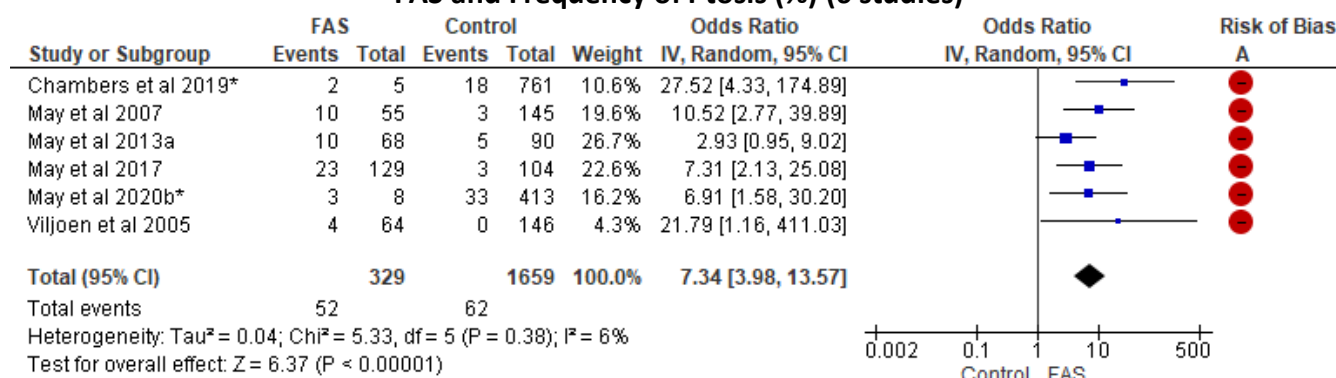
FASD and Frequency of Ptosis (%) (1 study)



Risk of bias legend

(A) Overall RoB

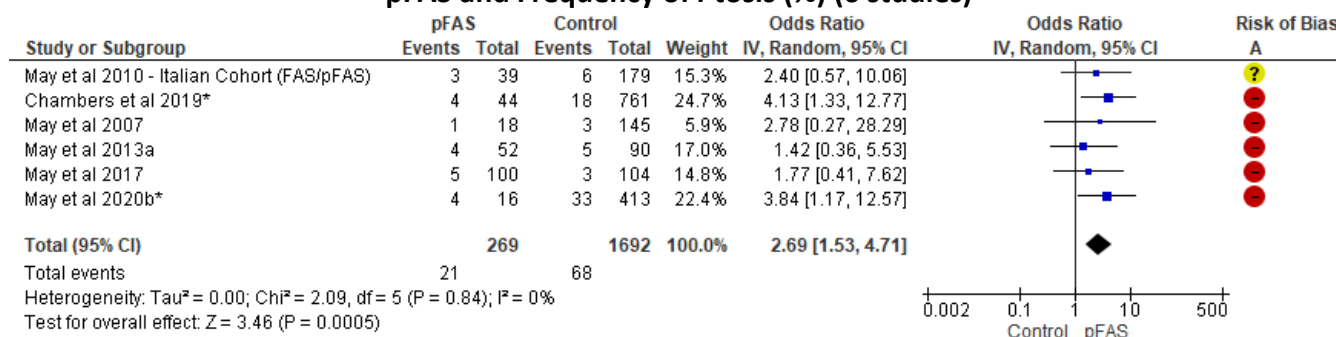
FAS and Frequency of Ptosis (%) (6 studies)



Risk of bias legend

(A) Overall RoB

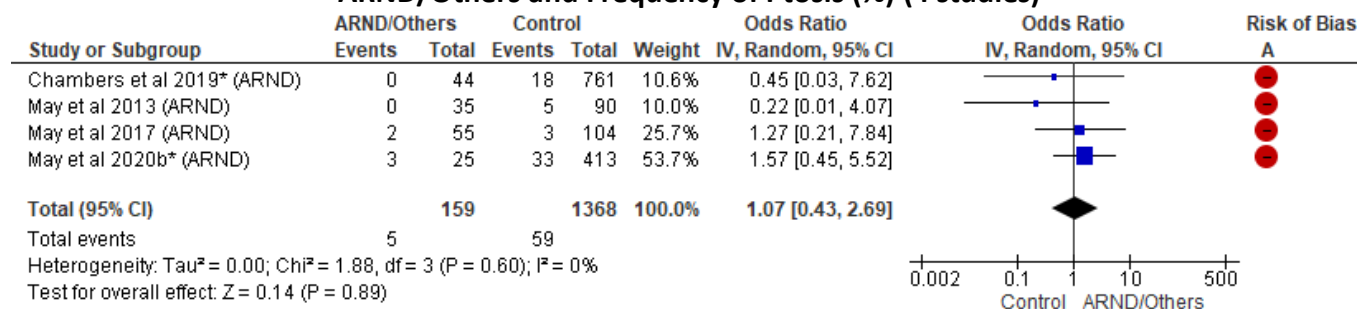
pFAS and Frequency of Ptosis (%) (6 studies)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

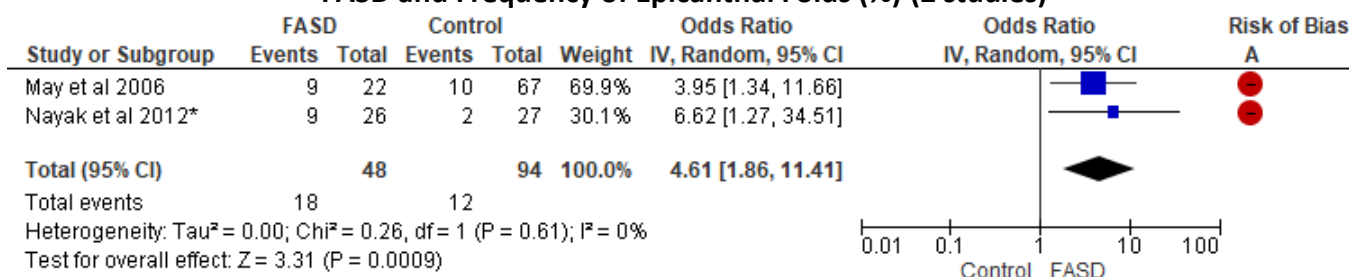
(A) Overall RoB

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

EPICANTHAL FOLDS

Epicanthal Folds (%)

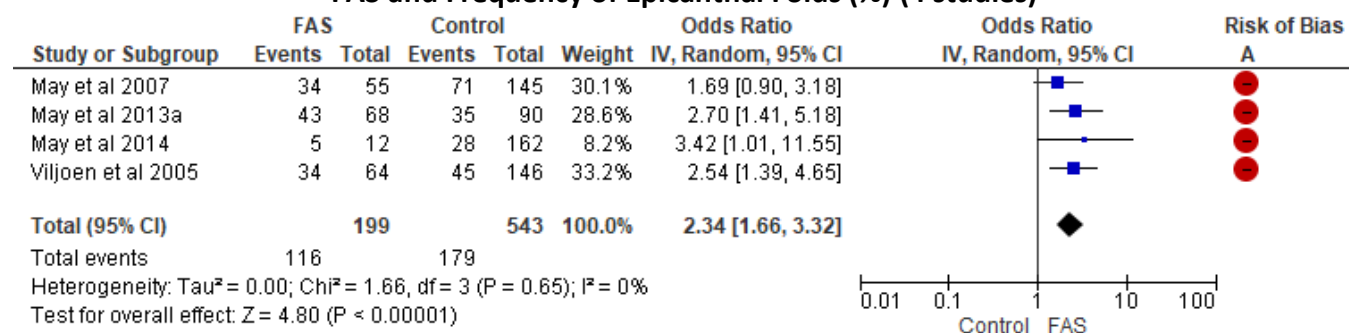
FASD and Frequency of Epicanthal Folds (%) (2 studies)



Risk of bias legend

(A) Overall RoB

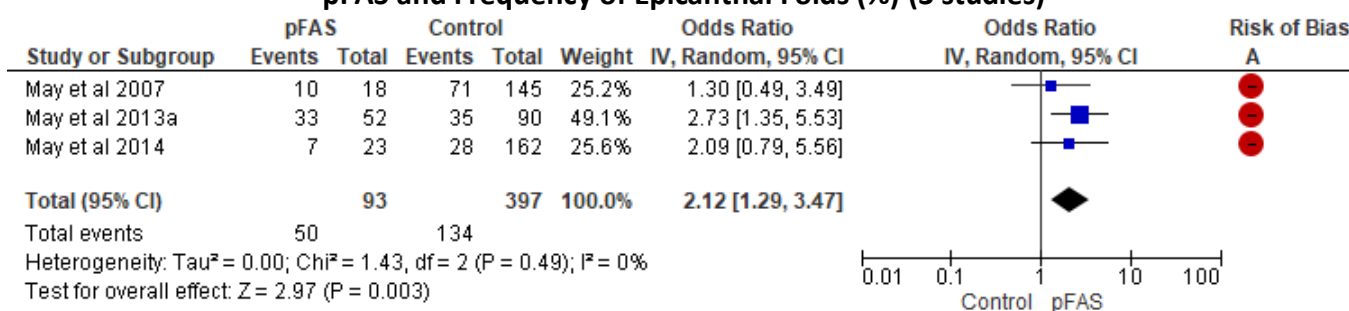
FAS and Frequency of Epicanthal Folds (%) (4 studies)



Risk of bias legend

(A) Overall RoB

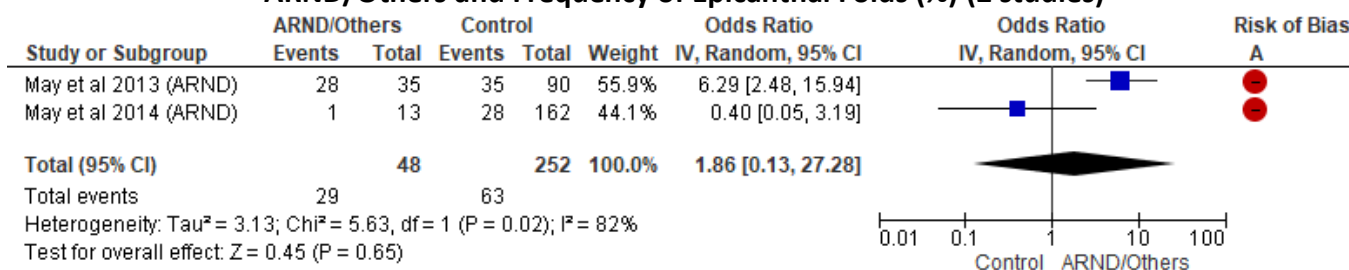
pFAS and Frequency of Epicanthal Folds (%) (3 studies)



Risk of bias legend

(A) Overall RoB

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



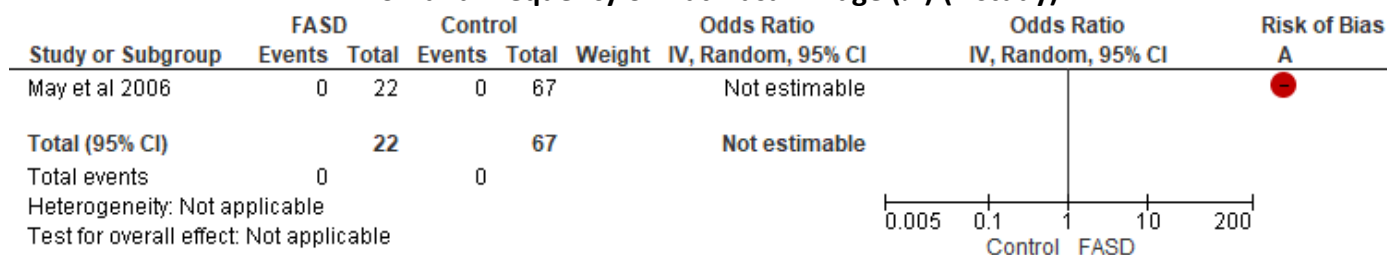
Risk of bias legend

(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 reports ARND and non-syndromal, used former.

Flat Nasal Bridge (%)

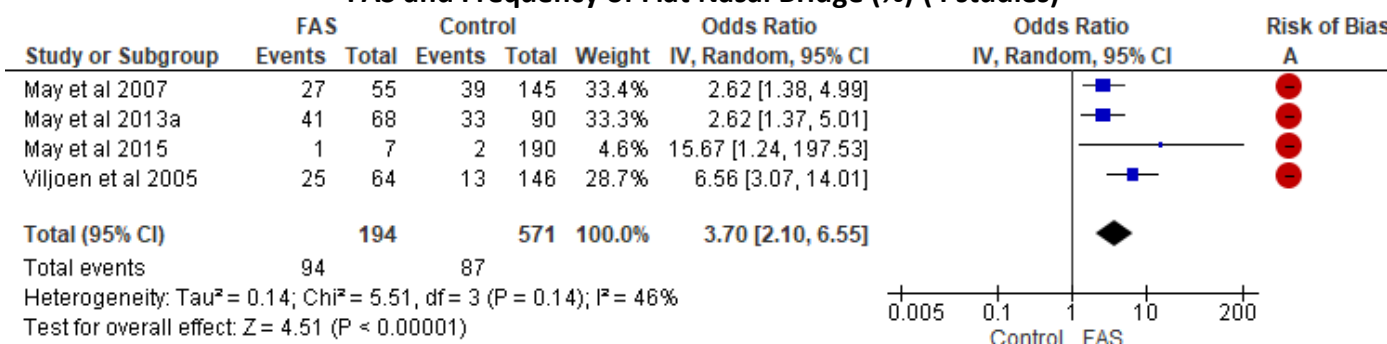
FASD and Frequency of Flat Nasal Bridge (%) (1 study)



Risk of bias legend

(A) Overall RoB

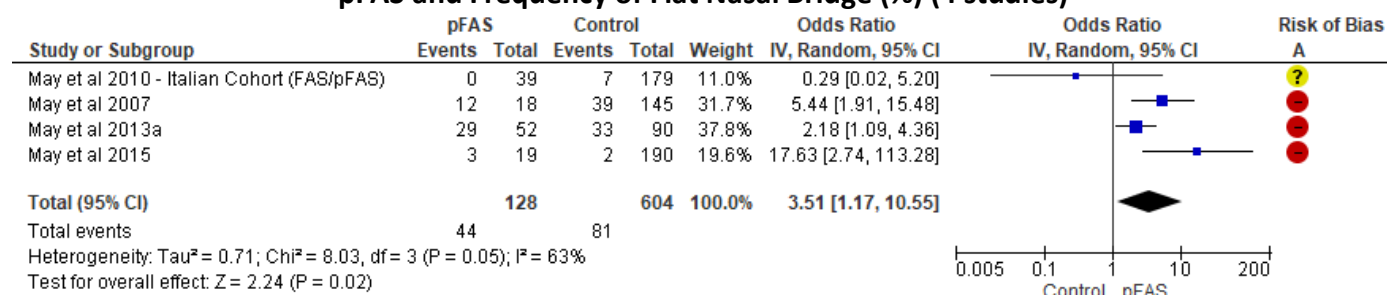
FAS and Frequency of Flat Nasal Bridge (%) (4 studies)



Risk of bias legend

(A) Overall RoB

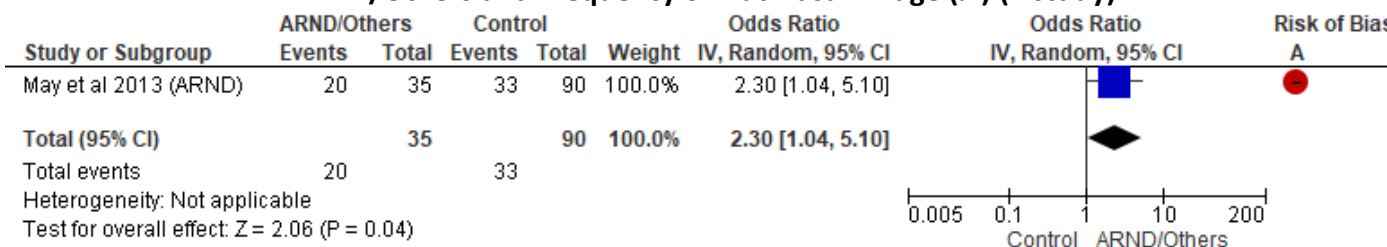
pFAS and Frequency of Flat Nasal Bridge (%) (4 studies)



Risk of bias legend

(A) Overall RoB

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



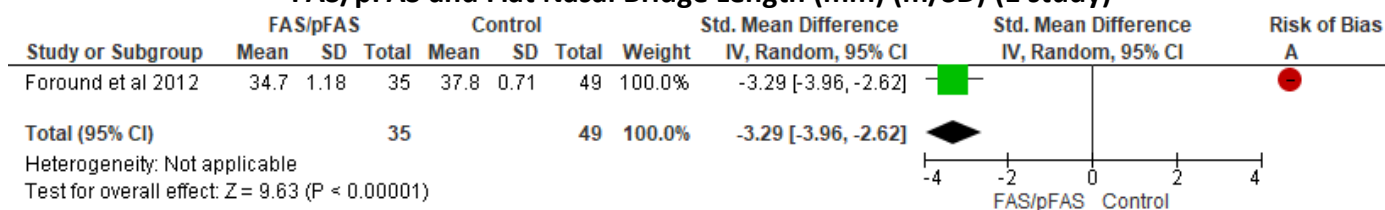
Risk of bias legend

(A) Overall RoB

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

Nasal Bridge Length (mm) (m/SD)

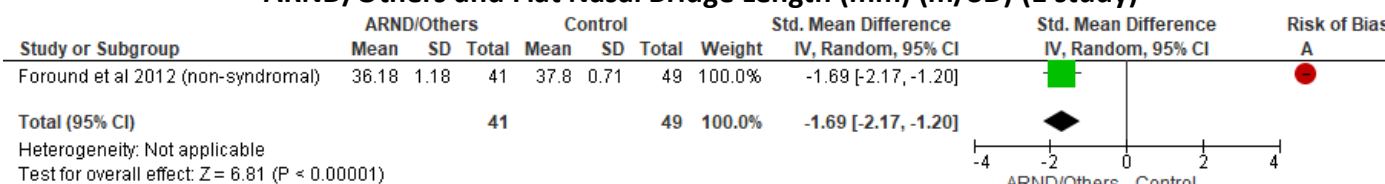
FAS/pFAS and Flat Nasal Bridge Length (mm) (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

ARND/Others and Flat Nasal Bridge Length (mm) (m/SD) (1 study)



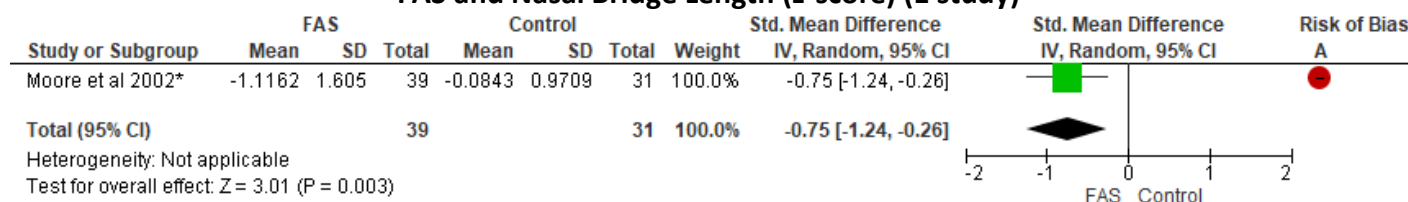
Risk of bias legend

(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.

Nasal Bridge Length (z-score)

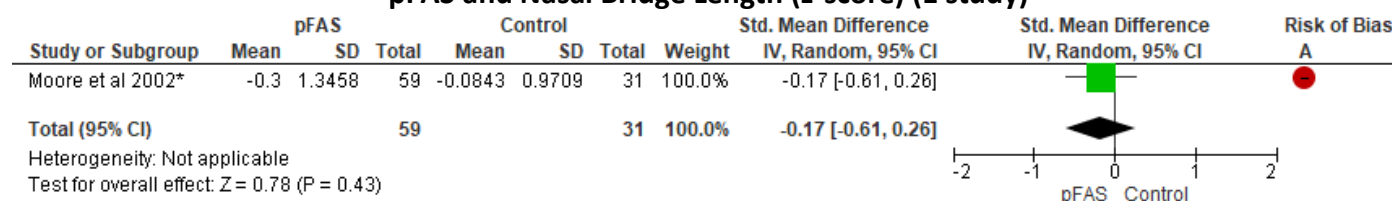
FAS and Nasal Bridge Length (z-score) (1 study)



Risk of bias legend

(A) Overall RoB

pFAS and Nasal Bridge Length (z-score) (1 study)



Risk of bias legend

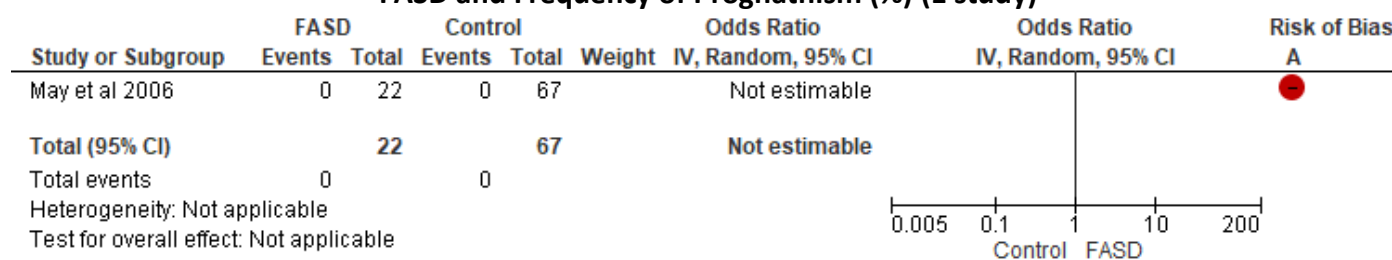
(A) Overall RoB

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

PROGNATHISM

Prognathism (%)

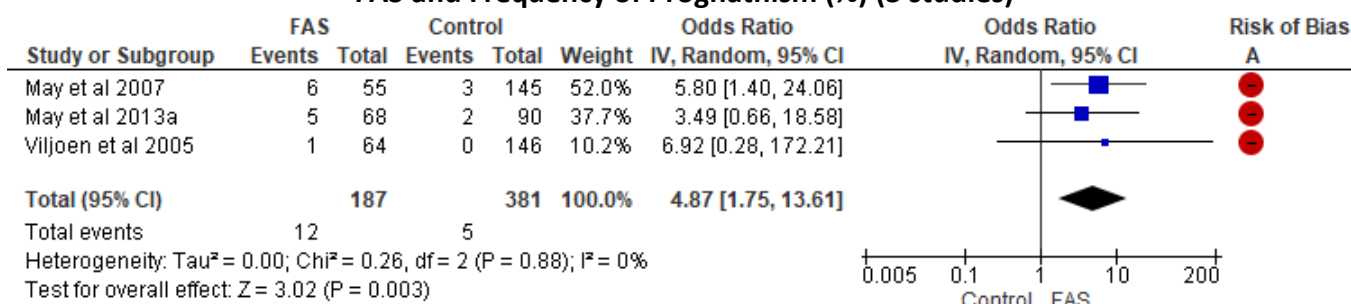
FASD and Frequency of Prognathism (%) (1 study)



Risk of bias legend

(A) Overall RoB

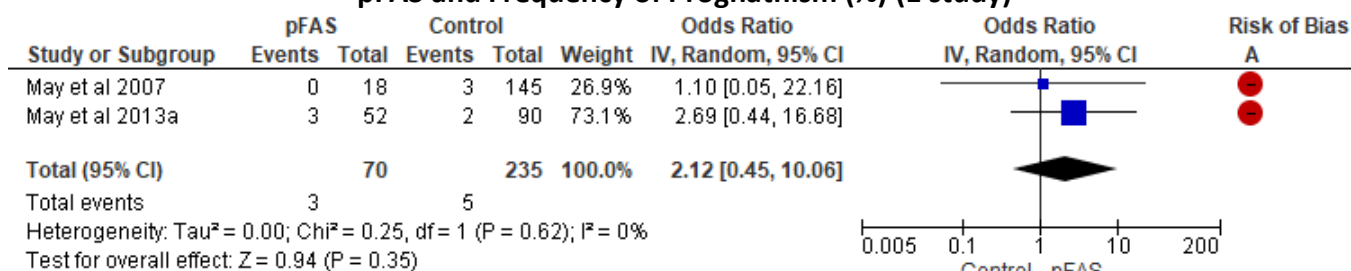
FAS and Frequency of Prognathism (%) (3 studies)



Risk of bias legend

(A) Overall RoB

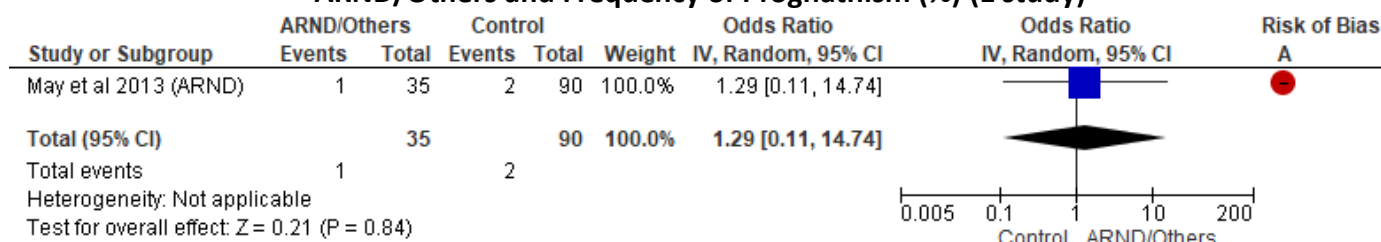
pFAS and Frequency of Prognathism (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

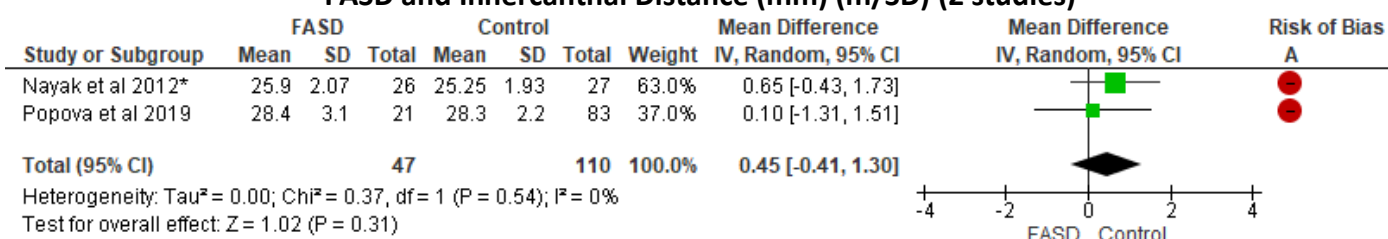
(A) Overall RoB

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

INNERCANTHAL DISTANCE

Innercanthal distance (mm) (m/SD)

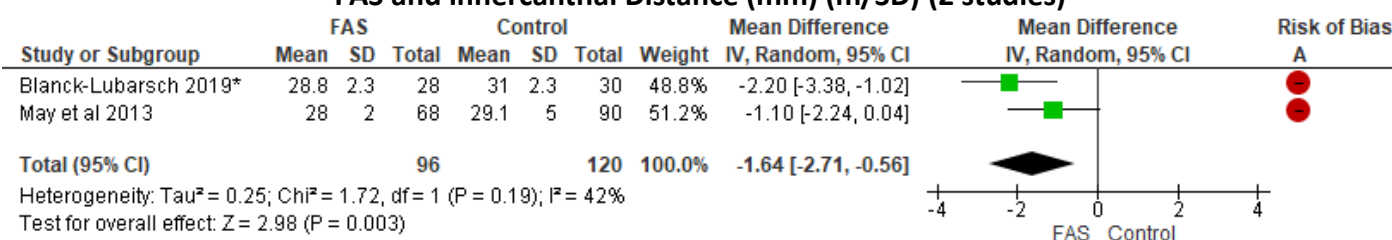
FASD and Innercanthal Distance (mm) (m/SD) (2 studies)



Risk of bias legend

(A) Overall RoB

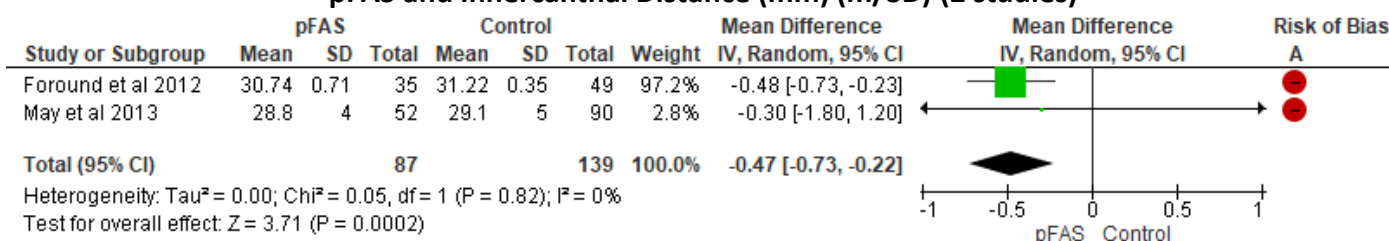
FAS and Innercanthal Distance (mm) (m/SD) (2 studies)



Risk of bias legend

(A) Overall RoB

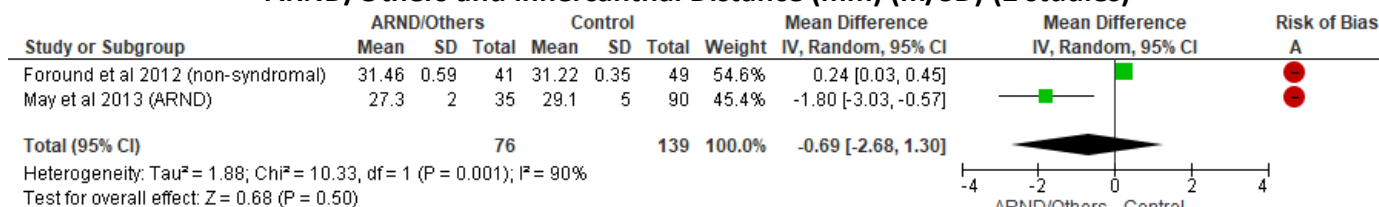
pFAS and Innercanthal Distance (mm) (m/SD) (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

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



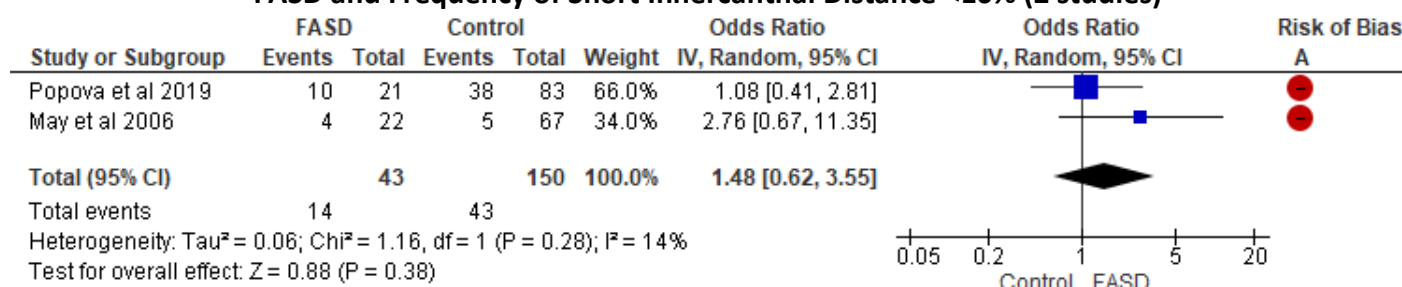
[Risk of bias legend](#)

(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 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 (%)

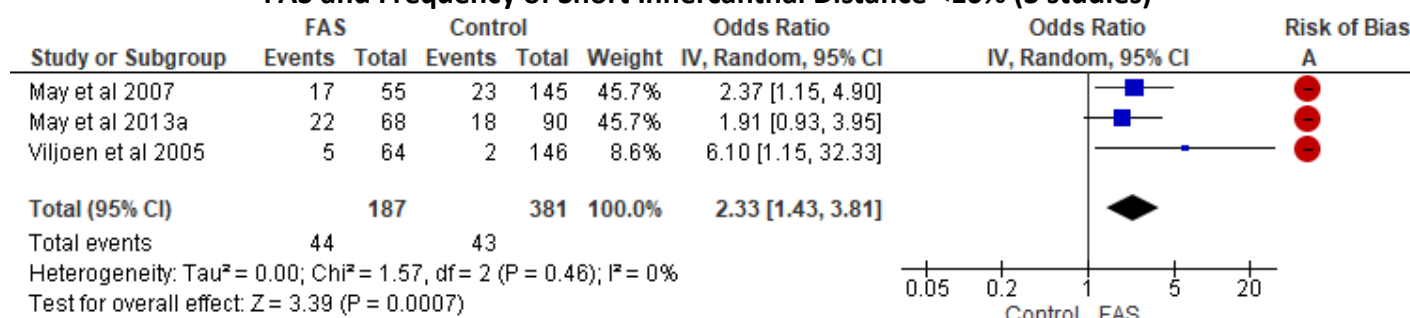
FASD and Frequency of Short Innercanthal Distance <10% (2 studies)



[Risk of bias legend](#)

(A) Overall RoB

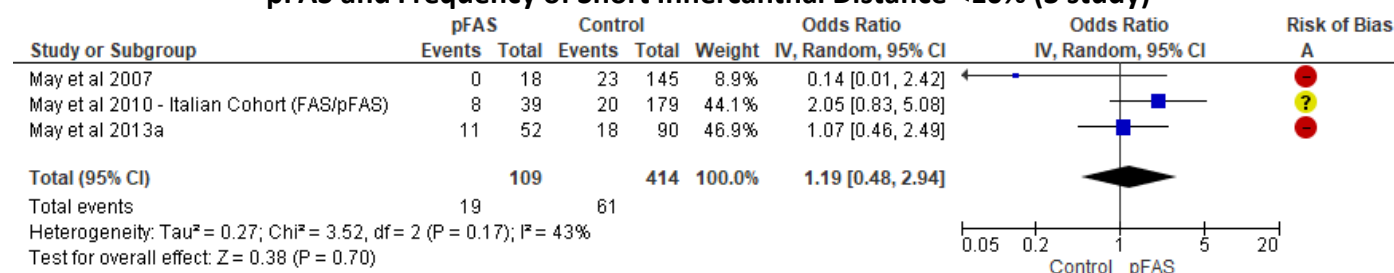
FAS and Frequency of Short Innercanthal Distance <10% (3 studies)



[Risk of bias legend](#)

(A) Overall RoB

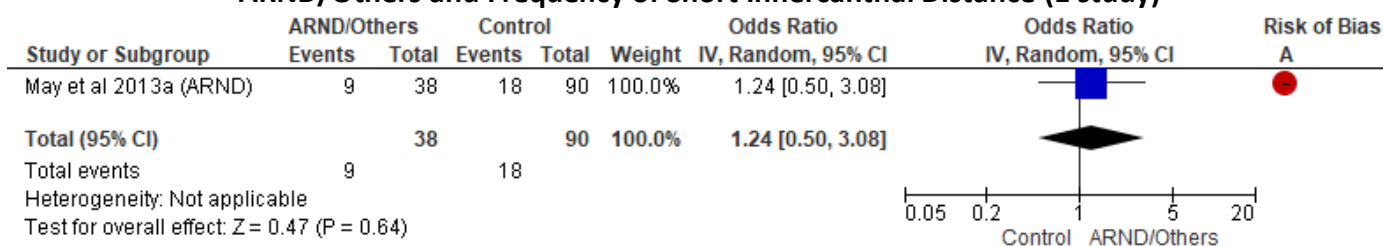
pFAS and Frequency of Short Innercanthal Distance <10% (3 study)



[Risk of bias legend](#)

(A) Overall RoB

ARND/Others and Frequency of Short Innercanthal Distance (1 study)



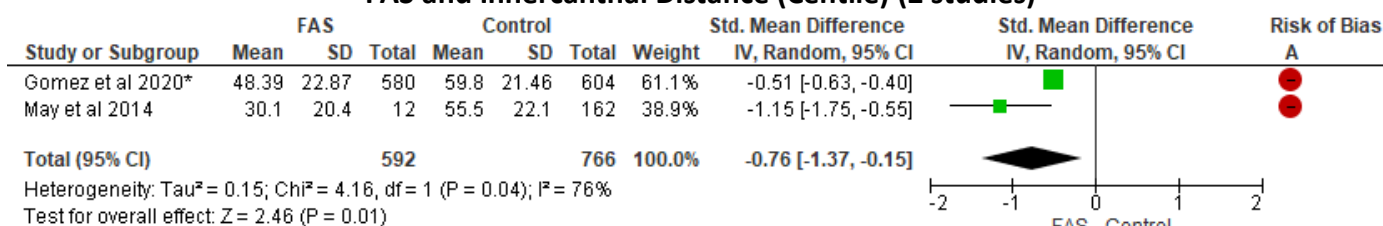
Risk of bias legend

(A) Overall RoB

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

Innercanthal Distance (centile)

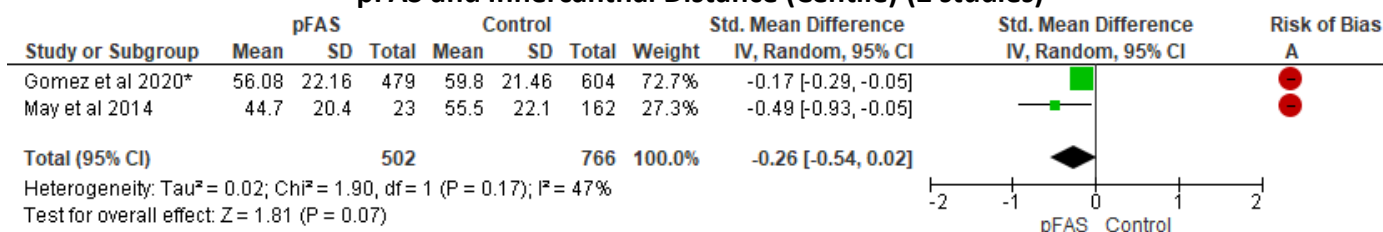
FAS and Innercanthal Distance (Centile) (2 studies)



Risk of bias legend

(A) Overall RoB

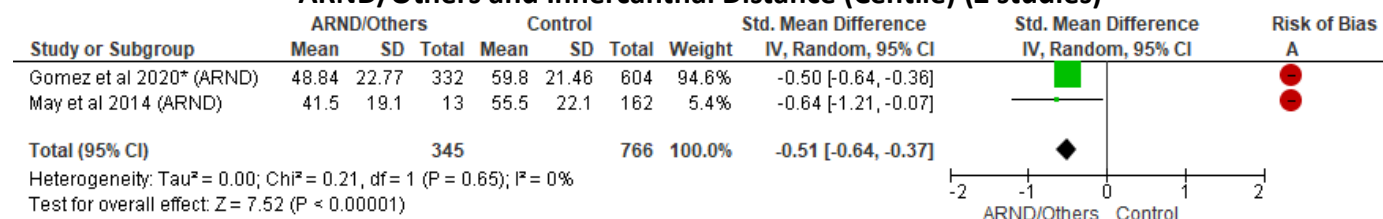
pFAS and Innercanthal Distance (Centile) (2 studies)



Risk of bias legend

(A) Overall RoB

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



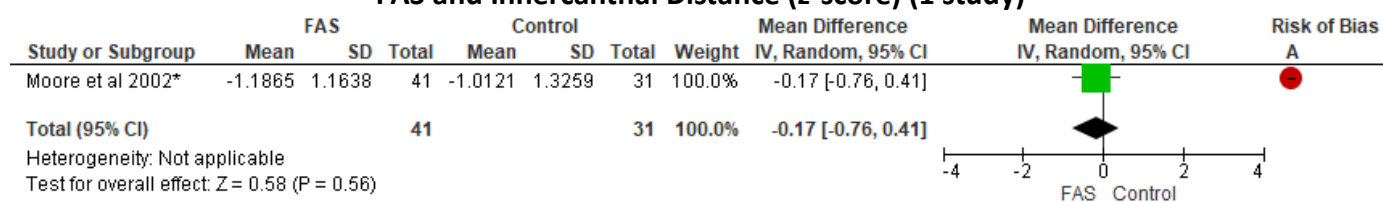
Risk of bias legend

(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)

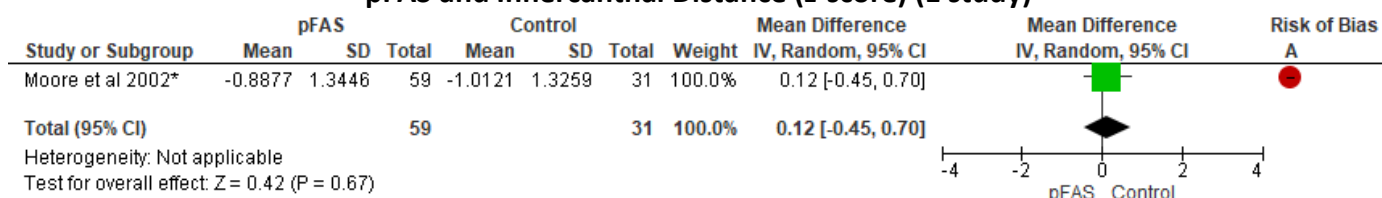
FAS and Innercanthal Distance (z-score) (1 study)



Risk of bias legend

(A) Overall RoB

pFAS and Innercanthal Distance (z-score) (1 study)



Risk of bias legend

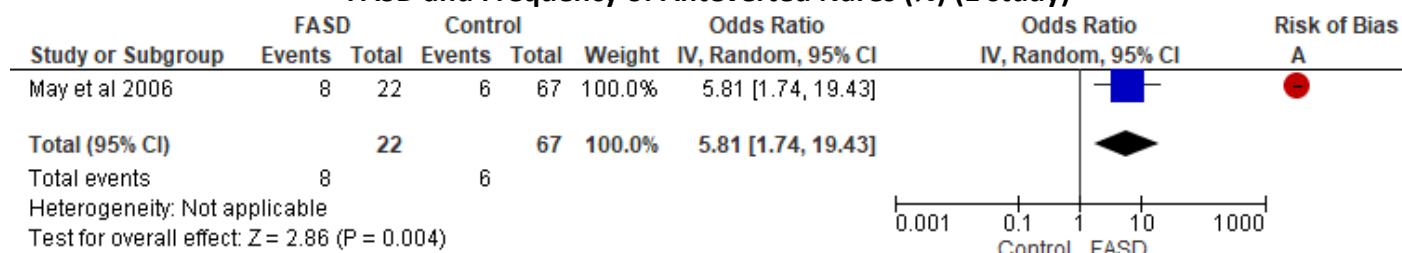
(A) Overall RoB

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

ANTEVERTED NARES

Anteverted Nares (%)

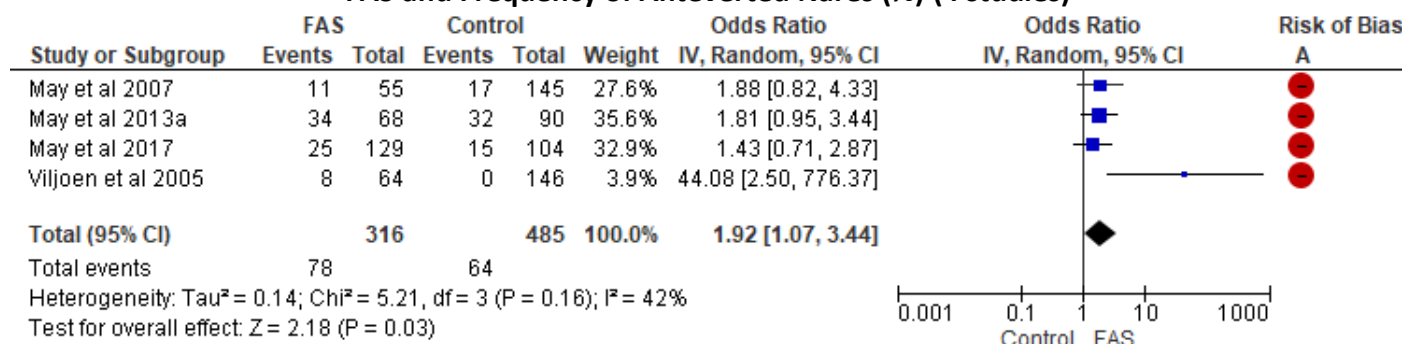
FASD and Frequency of Anteverted Nares (%) (1 study)



Risk of bias legend

(A) Overall RoB

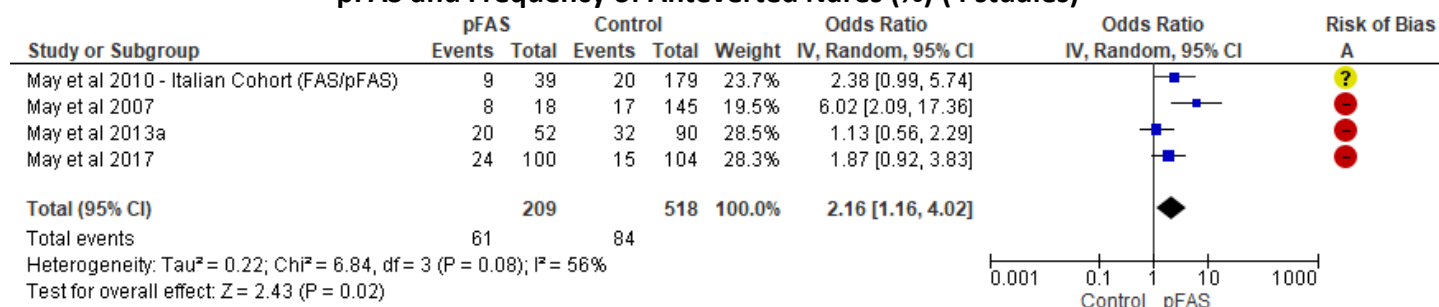
FAS and Frequency of Anteverted Nares (%) (4 studies)



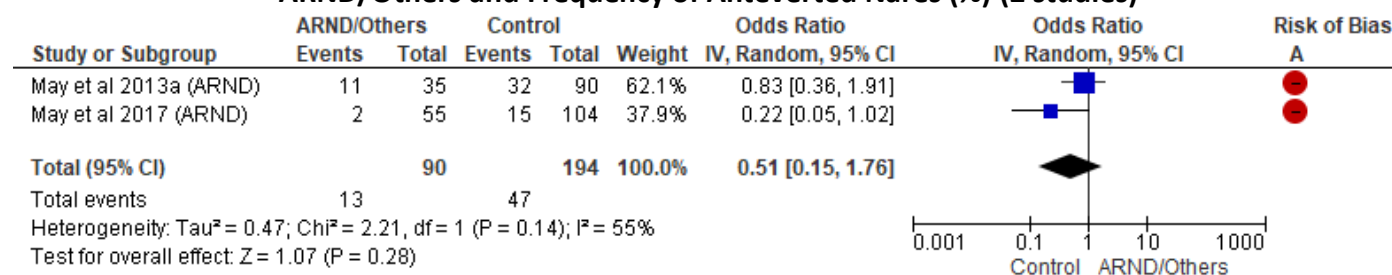
Risk of bias legend

(A) Overall RoB

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



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

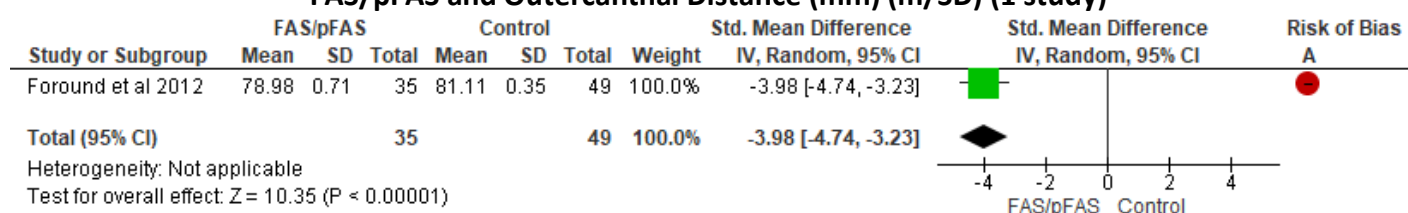


Notes: All unmarked studies use dysmorphology assessment described by Hoyne 2005. May et al 2013a reports ARND and non-syndromal, used former.

OUTERCANTHAL DISTANCE

Outer canthal distance (mm) (m/SD)

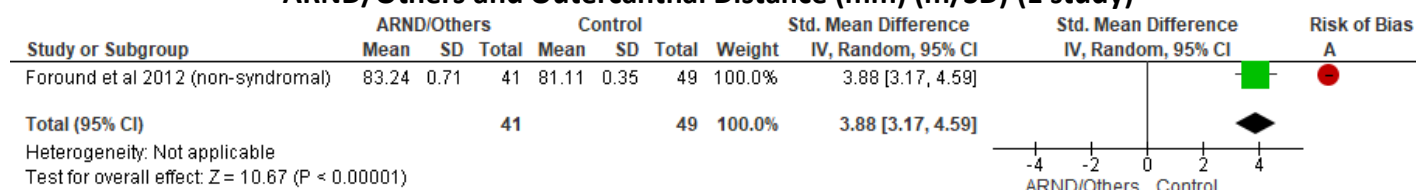
FAS/pFAS and Outer canthal Distance (mm) (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

ARND/Others and Outer canthal Distance (mm) (m/SD) (1 study)



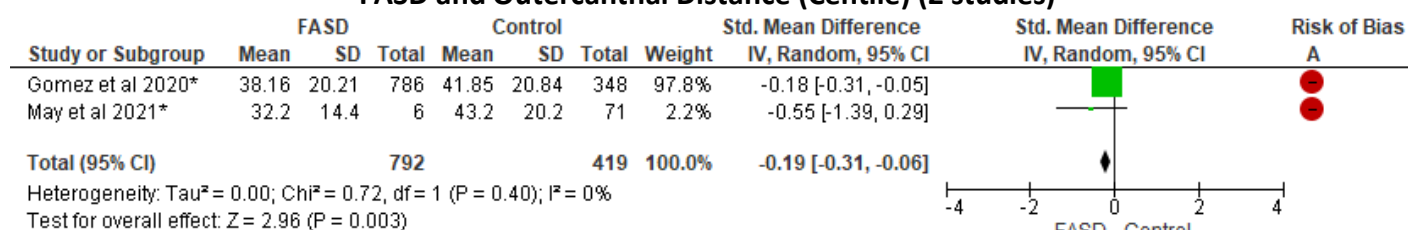
Risk of bias legend

(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.

Outer canthal Distance (Centile)

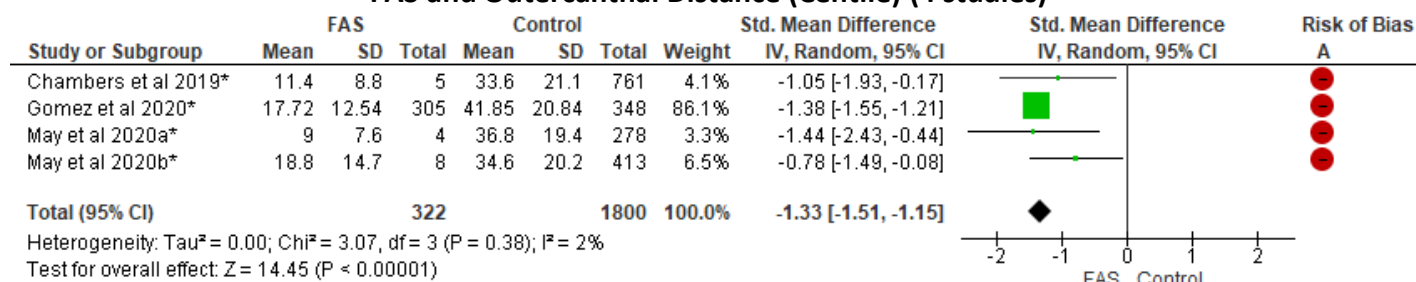
FASD and Outer canthal Distance (Centile) (2 studies)



Risk of bias legend

(A) Overall RoB

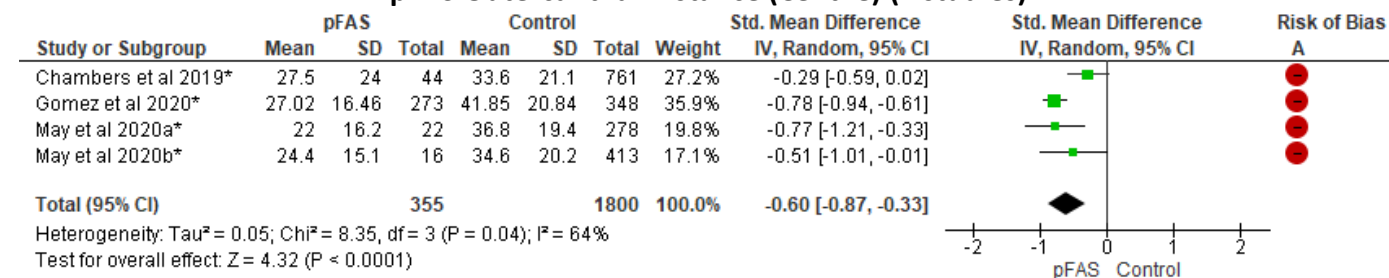
FAS and Outer canthal Distance (Centile) (4 studies)



Risk of bias legend

(A) Overall RoB

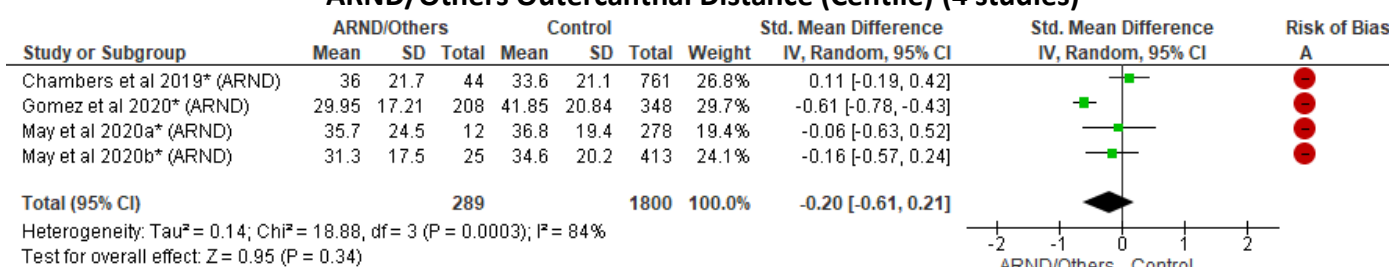
pFAS Outer canthal Distance (Centile) (4 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others Outercanthal Distance (Centile) (4 studies)



Risk of bias legend

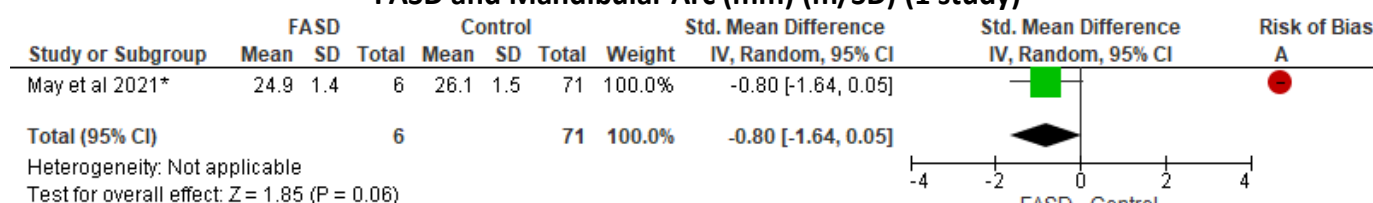
(A) Overall RoB

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

MANDIBULAR ARC

Mandibular Arc (mm) (m/SD)

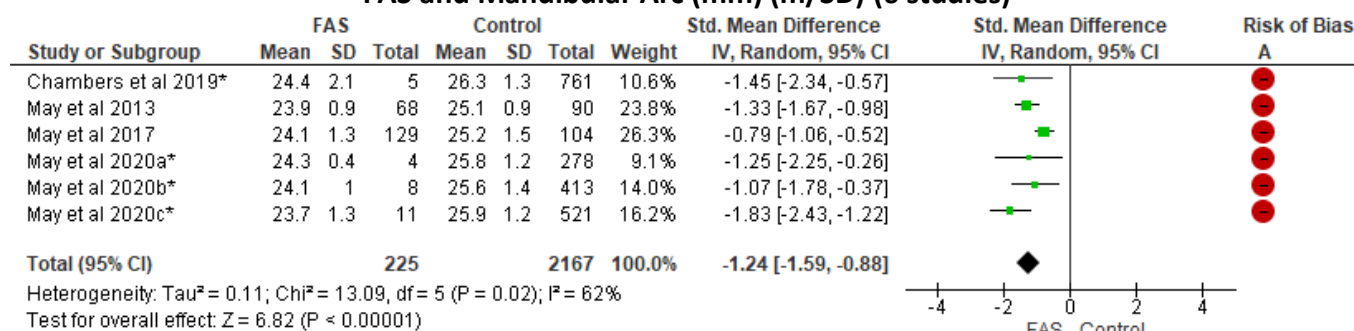
FASD and Mandibular Arc (mm) (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

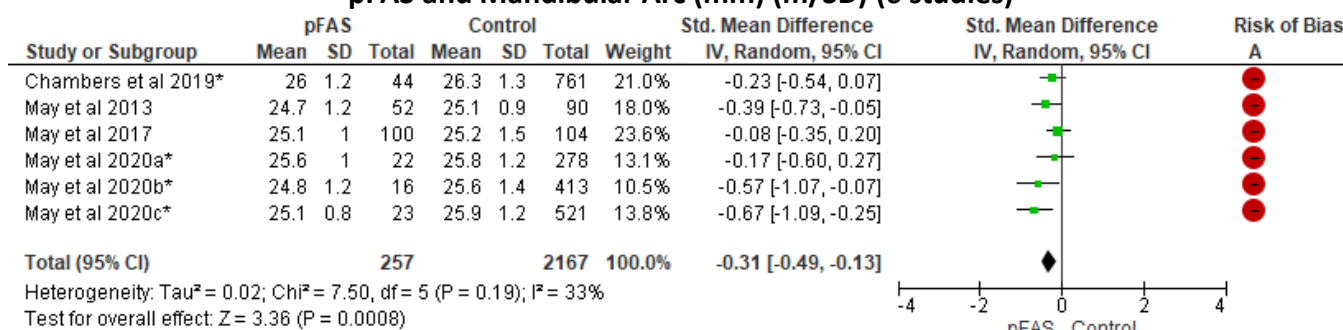
FAS and Mandibular Arc (mm) (m/SD) (6 studies)



Risk of bias legend

(A) Overall RoB

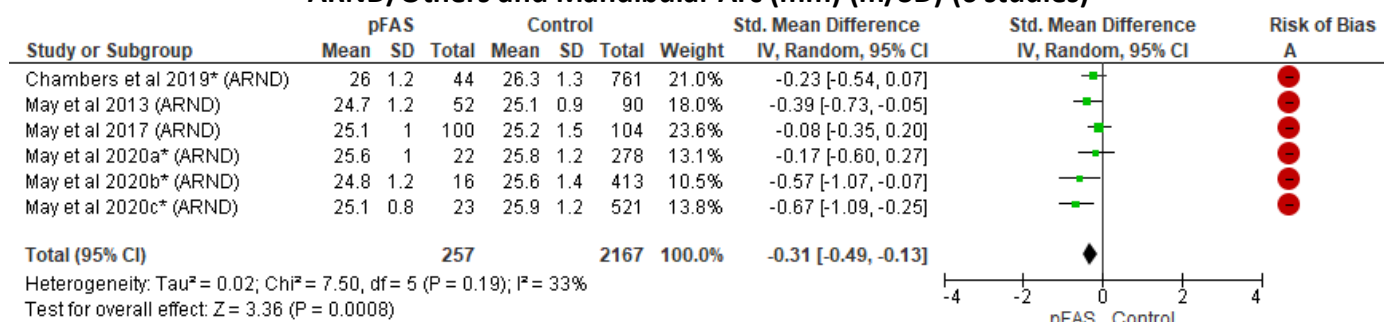
pFAS and Mandibular Arc (mm) (m/SD) (6 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Mandibular Arc (mm) (m/SD) (6 studies)



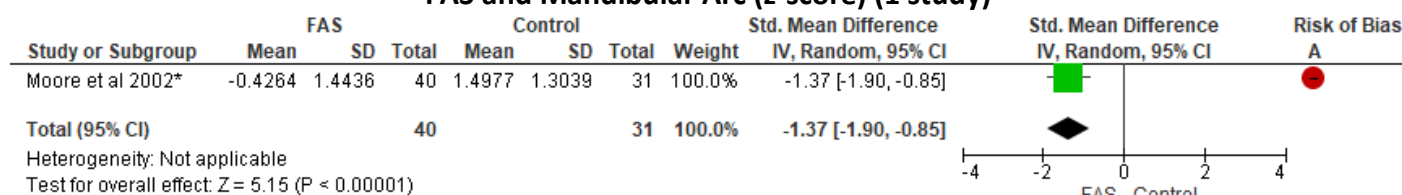
Risk of bias legend

(A) Overall RoB

Notes: * indicates dysmorphology assessment other than Hoyme 2005.

Mandibular Arc (z-score)

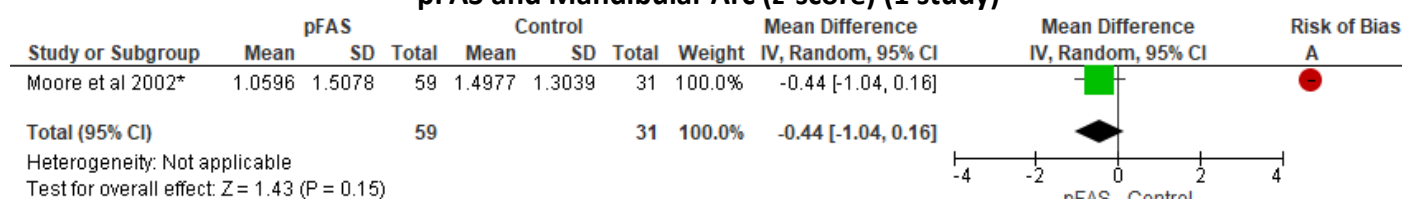
FAS and Mandibular Arc (z-score) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

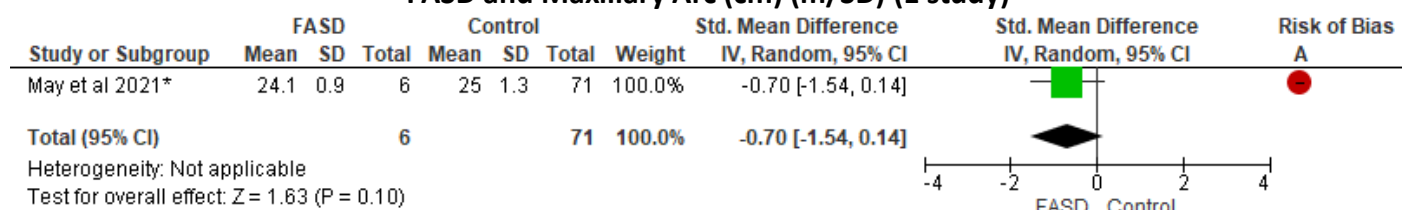
(A) Overall RoB

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

MAXILLARY ARC

Maxillary Arc (cm) (m/SD)

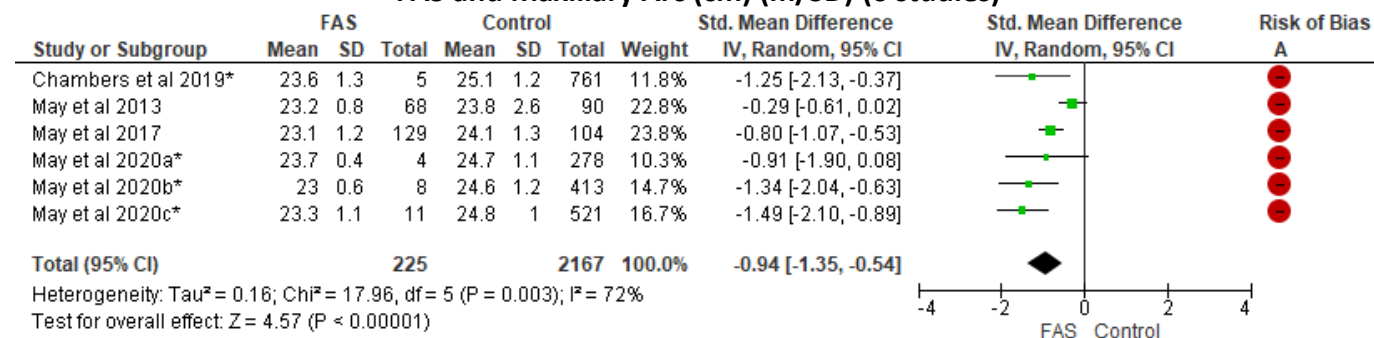
FASD and Maxillary Arc (cm) (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

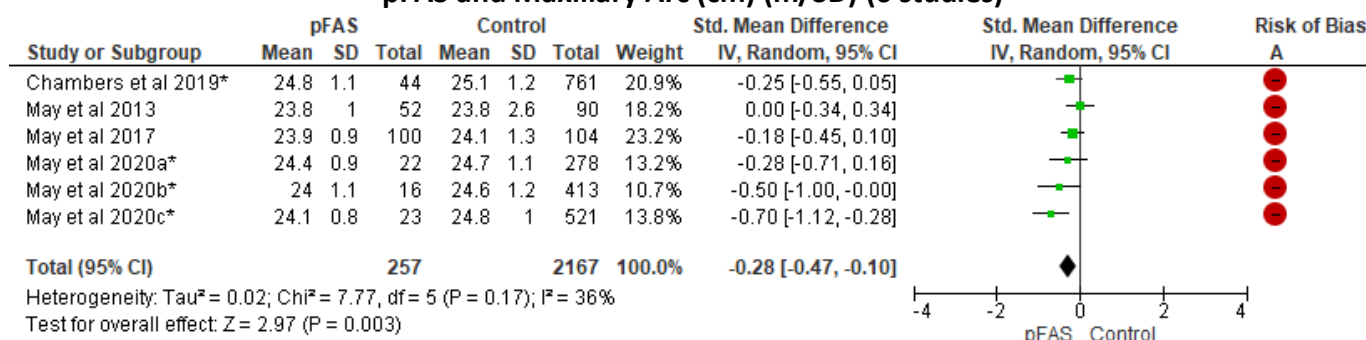
FAS and Maxillary Arc (cm) (m/SD) (6 studies)



Risk of bias legend

(A) Overall RoB

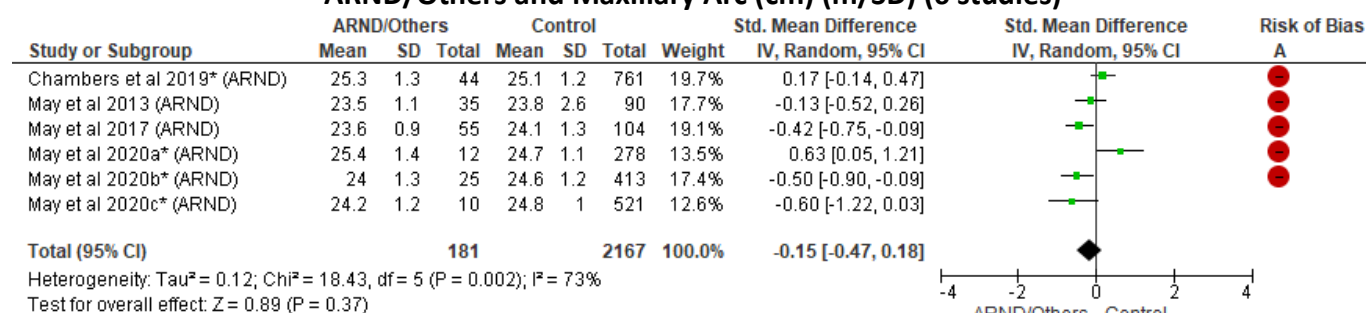
pFAS and Maxillary Arc (cm) (m/SD) (6 studies)



Risk of bias legend

(A) Overall RoB

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



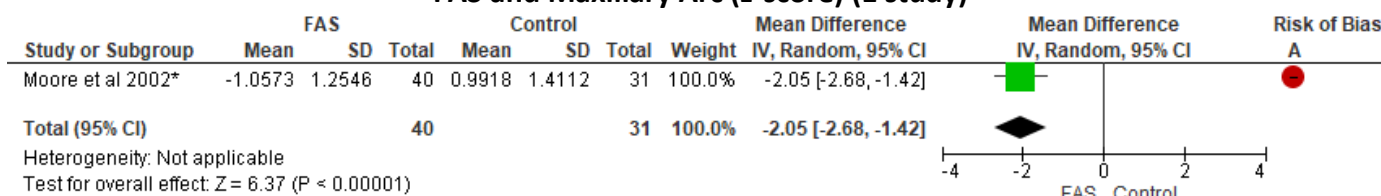
Risk of bias legend

(A) Overall RoB

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

Maxillary Arc (z-score)

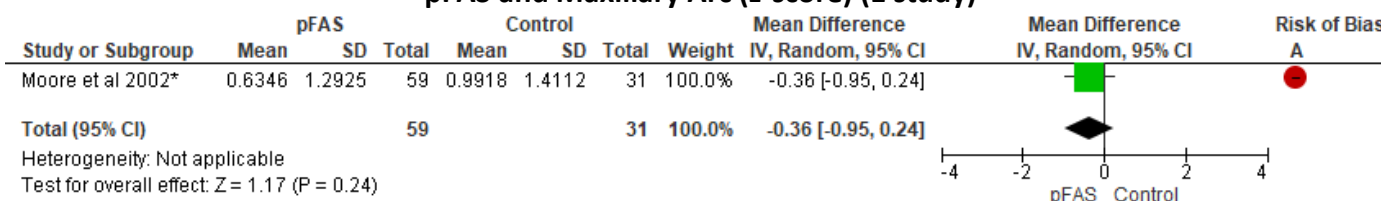
FAS and Maxillary Arc (z-score) (1 study)



Risk of bias legend

(A) Overall RoB

pFAS and Maxillary Arc (z-score) (1 study)



Risk of bias legend

(A) Overall RoB

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

Summary of available outcomes for other minor non-facial features

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

GRADE ratings for other minor features

	Certainty assessment					№ of patients		Effect		Certainty
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
HEART PROBLEMS										
Heart Defect (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	4/45	5/253	OR 4.84 (1.25 to 18.77)	-	⊕⊕○○ Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	4/19 (21.1%)	5/253 (2.0%)	OR 13.23 (3.22 to 54.41)	191 more per 1,000 (from 41 more to 503 more)	⊕⊕○○ Low
Confirmed Unquantifiable										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	12	12	OR 5.50 (0.51 to 59.01)	-	⊕○○○ Very low
Heart Murmur (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	9/45	19/253	OR 3.08 (1.29 to 7.33)	-	⊕⊕○○ Low
Very Heavy PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	9/19 (47.4%)	19/253 (7.5%)	OR 11.08 (4.02 to 30.58)	-	⊕⊕○○ Low
HYPERTRICHOSIS (0 STUDIES)										
HYPOPLASTIC NAILS										
Hypoplastic Nails (%)										
Confirmed Unquantifiable										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	5/12 (41.7%)	0/12 (0.0%)	OR 18.33 (0.88 to 380.70)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low
CAMPTODACTYLY (%)										
Camptodactyly (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/45	4/253	OR 1.41 (0.15 to 12.96)		⊕○○○ Very low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/19 (5.3%)	2/253 (1.6%)	OR 3.46 (0.37 to 32.58)		⊕○○○ Very low
EAR ABNORMALITIES										
Railroad track ears (%)										
Moderate PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	4/45	19/253	OR 1.20 (0.39 to 3.71)		⊕○○○ Very low
Very Heavy PAE										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	1/19	19/253	OR 0.68 (0.09 to 5.41)		⊕○○○ Very low

FASD										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	0/22 (0.0%)	1/67 (1.5%)	OR 0.99 (0.04 to 25.06)	0 fewer per 1,000 (from 14 fewer to 260 more)	⊕○○○ Very low
FAS										
5	serious ^a	not serious	serious ^c	serious ^{e,f}	none	26/199 (13%)	27/1332 (2.02%)	OR 4.95 (2.32 to 10.53)	-	⊕⊕○○ Low
pFAS										
5	serious ^a	not serious	not serious	serious ^{e,f}	none	14/172 (8.1%)	29/1365 (2.1%)	OR 3.12 (1.53 to 6.38)	-	⊕○○○ Very low
ARND/Others										
2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	4/79 (5.1%)	20/851 (2.4%)	OR 1.29 (0.40 to 4.20)	7 more per 1,000 (from 14 fewer to 68 more)	⊕○○○ Very low
HYPERTRICHOSIS										
Hypertrichosis (%)										
FASD										
1	serious ^a	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	not estimable	-	N/A
FAS (one study non-estimable)										
3	serious ^a	not serious	not serious	serious ^{e,f}	none	3/126 (2.3%)	4/481 (0.83%)	OR 6.99 (1.27 to 38.45)	-	⊕⊕○○ Low
pFAS										
1	serious ^a	not serious	serious ^c	very serious ^{d,e,f}	none	1/18 (5.6%)	0/145 (0.0%)	OR 24.94 (0.98 to 636.12)	-	⊕○○○ Very low
HYPOPLASTIC NAILS (%)										
Hypoplastic Nails (%)										
FASD										
1	serious ^a	not serious	not serious	N/A	none	0/22 (0.0%)	0/67 (0.0%)	not estimable	-	N/A
FAS										
4	serious ^a	not serious	not serious	serious ^{e,f}	none	10/135 (7.4%)	6/926 (0.65%)	OR 5.50 (1.82 to 16.68)	-	⊕⊕○○ Low
pFAS										
4	serious ^a	not serious	not serious	serious ^{e,f}	none	5/108 (4.6%)	6/926 (0.65%)	OR 5.42 (1.59 to 18.41)	-	⊕⊕○○ Low
ARND/Others										
3	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	2/72 (3.3%)	4/781 (0.8%)	OR 2.82 (0.53 to 15.07)	14 more per 1,000 (from 4 fewer to 1000 more)	⊕○○○ Very low
CAMPTODACTYLY										
Camptodactyly (%)										
FASD										
1	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	5/22 (22.7%)	5/67 (7.5%)	OR 3.65	153 more per 1,000 (from 4	⊕○○○ Very low

2	serious ^a	not serious	not serious	very serious ^{d,e,f}	none	0/79 (0.0%)	22/851 (2.6%)	OR 0.54 (0.06 to 4.52)	12 fewer per 1,000 (from 24 fewer to 81 more)	⊕○○○ Very low
ALTERED PALMAR CREASE										
Altered Palmar Crease (%)										
FASD										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	13/48 (27.1%)	14/94 (14.9%)	OR 3.45 (1.34 to 8.88)	228 more per 1,000 (from 41 to 460 more)	⊕⊕○○ Low
FAS										
6	serious ^a	not serious	serious ^c	serious ^f	none	145/332 (43.67%)	132/176 7 (7.4%)	OR 3.29 (2.16 to 5.00)	-	⊕○○○ Very low
pFAS										
6	serious ^a	not serious	not serious	serious ^f	none	73/267 (27.3%)	148/180 0 (8.2%)	OR 2.00 (1.25 to 3.19)	-	⊕⊕○○ Low
ARND/Others										
4	serious ^a	not serious	not serious	serious ^f	none	30/144 (2.08%)	68/1476 (4.6%)	OR 1.69 (1.00 to 2.86)	29 more per 1,000 (from 0 fewer to 75 more)	⊕⊕○○ Low
5th FINGER CLINODACTYLY										
5th Finger Clinodactyly (%)										
FASD										
2	serious ^a	not serious	not serious	serious ^{d,f}	none	10/48 (20.8%)	19/94 (20.2%)	OR 1.50 (0.58 to 3.89)	73 more per 1,000 (from 74 fewer to 294 more)	⊕⊕○○ Low
FAS										
5	serious ^a	not serious	serious ^c	serious ^{d,f}	none	95/206 (45.11%)	260/733 (35.47%)	OR 1.15 (0.81 to 1.63)	-	⊕○○○ Very low
pFAS										
5	serious ^a	not serious	not serious	serious ^f	none	89/151 (58.9%)	282/766 (36.8%)	OR 2.08 (1.24 to 3.48)	-	⊕⊕○○ Low
ARND/Others										
2	serious ^a	serious ^b	not serious	serious ^{d,f}	none	22/48 (45.8%)	105/252 (41.7%)	OR 0.81 (0.27 to 2.50)	50 fewer per 1,000 (from 255 fewer to 224 more)	⊕○○○ 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.

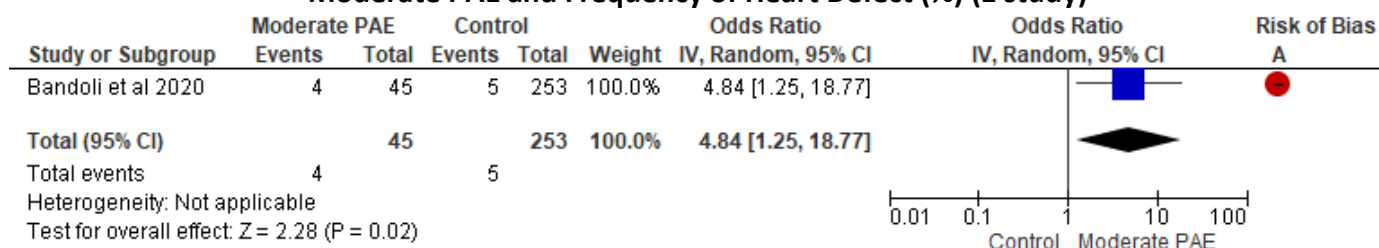
Meta-analyses for minor non-facial features

Exposure Studies

CARDIAC PROBLEMS

Heart Defect (%)

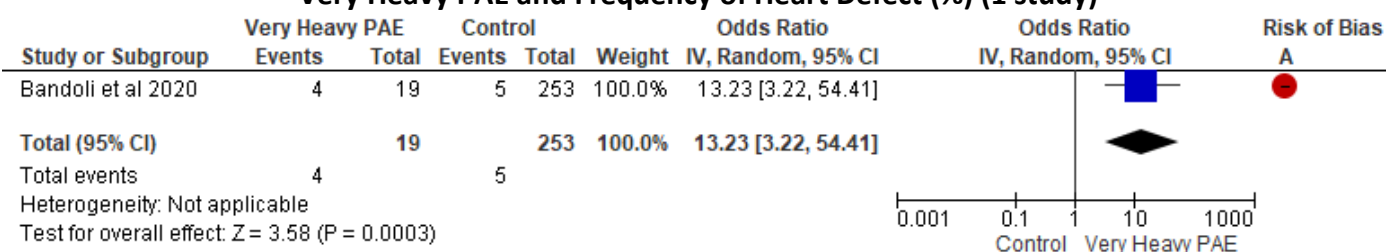
Moderate PAE and Frequency of Heart Defect (%) (1 study)



Risk of bias legend

(A) Overall RoB

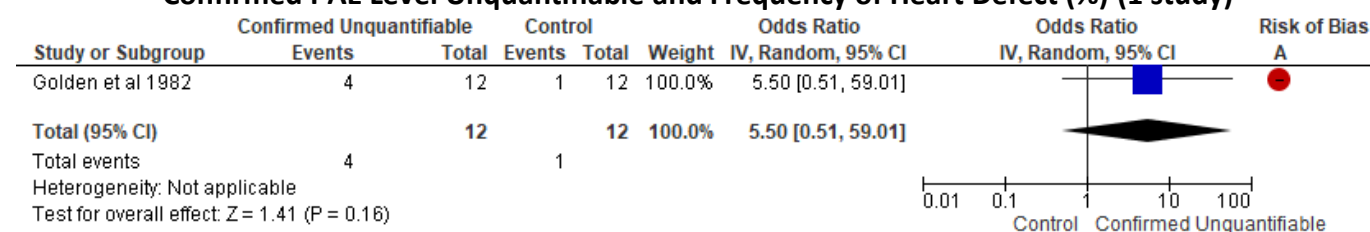
Very Heavy PAE and Frequency of Heart Defect (%) (1 study)



Risk of bias legend

(A) Overall RoB

Confirmed PAE Level Unquantifiable and Frequency of Heart Defect (%) (1 study)



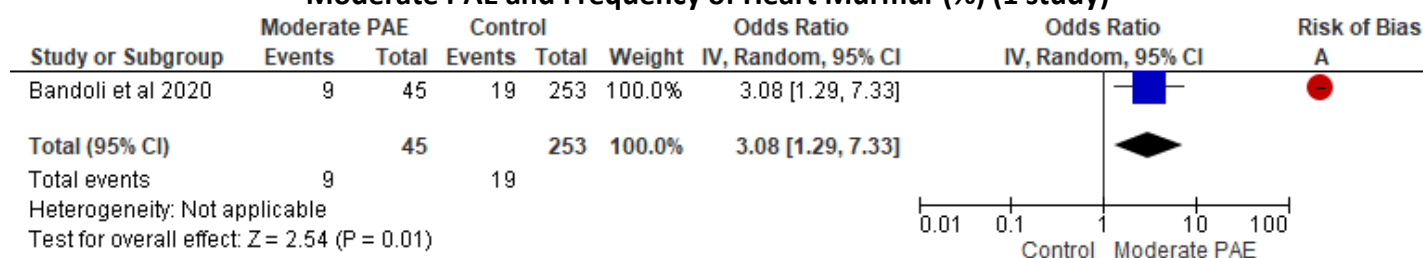
Risk of bias legend

(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.

Heart Murmur (%)

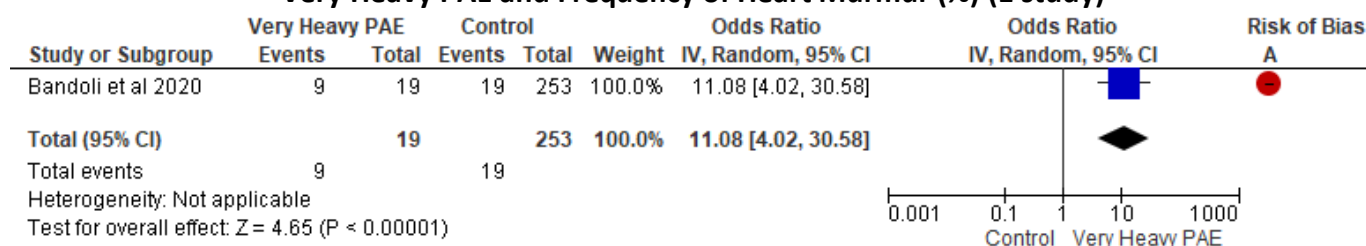
Moderate PAE and Frequency of Heart Murmur (%) (1 study)



Risk of bias legend

(A) Overall RoB

Very Heavy PAE and Frequency of Heart Murmur (%) (1 study)



Risk of bias legend

(A) Overall RoB

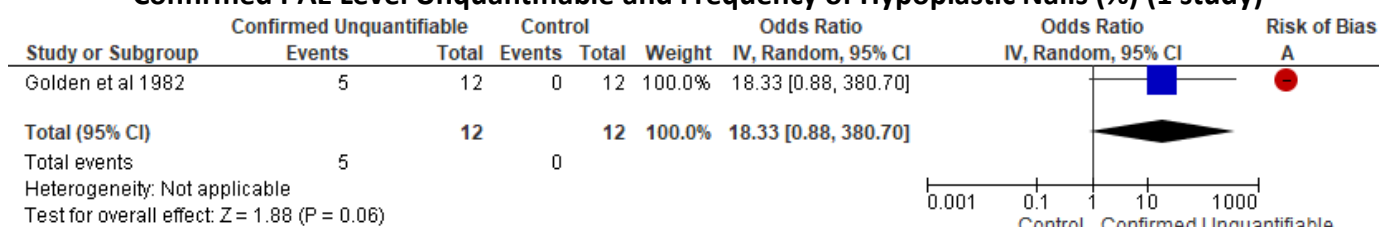
Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

HYPERTRICHOSIS (0 STUDIES)

HYPOPLASTIC NAILS

Hypoplastic Nails (%)

Confirmed PAE Level Unquantifiable and Frequency of Hypoplastic Nails (%) (1 study)



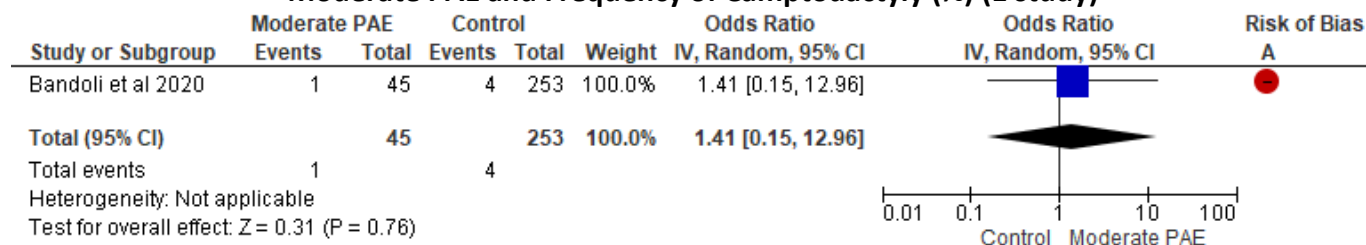
Risk of bias legend

(A) Overall RoB

CAMPTODACTYLY

Camptodactyly (%)

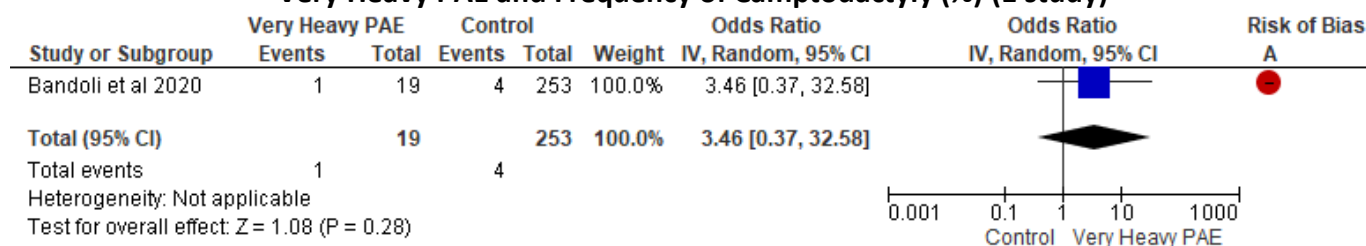
Moderate PAE and Frequency of Camptodactyly (%) (1 study)



Risk of bias legend

(A) Overall RoB

Very Heavy PAE and Frequency of Camptodactyly (%) (1 study)



Risk of bias legend

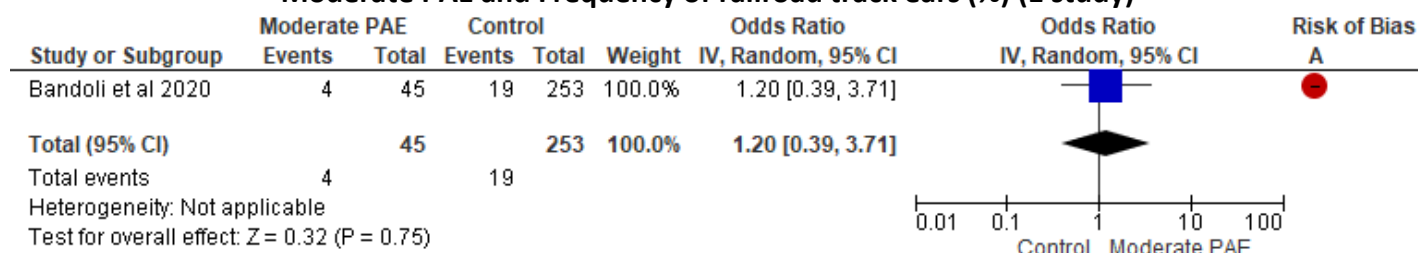
(A) Overall RoB

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

Railroad Track ears (%)

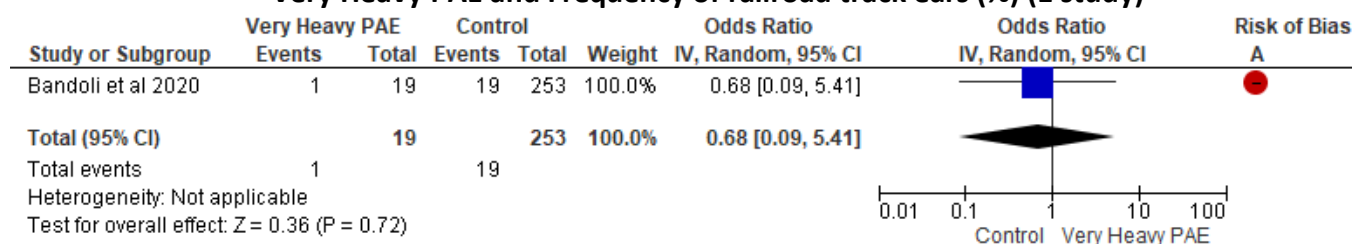
Moderate PAE and Frequency of railroad track ears (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

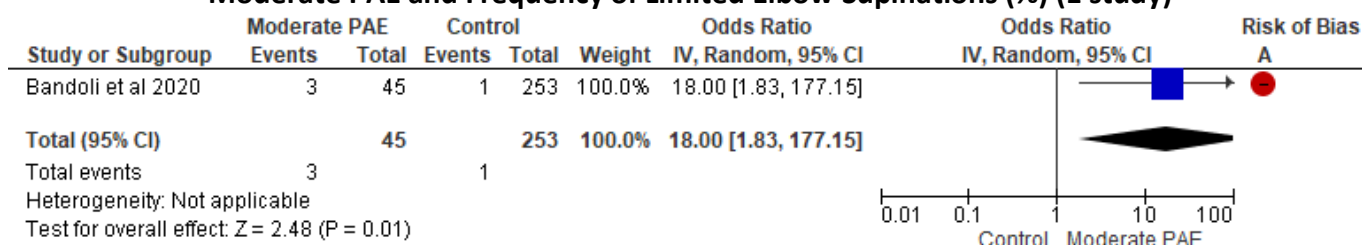
(A) Overall RoB

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 (%)

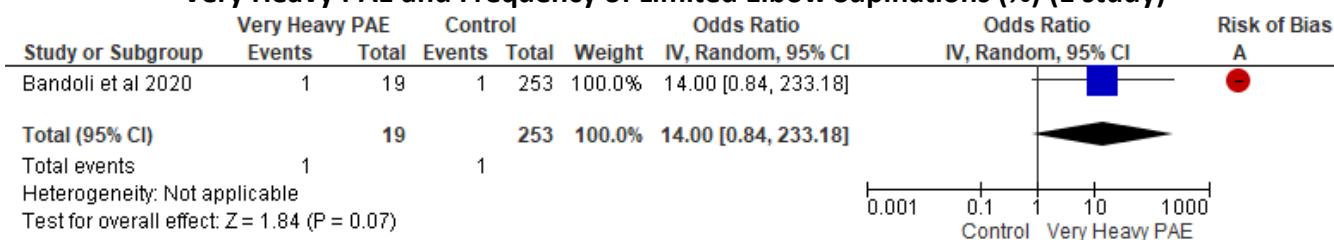
Moderate PAE and Frequency of Limited Elbow Supinations (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

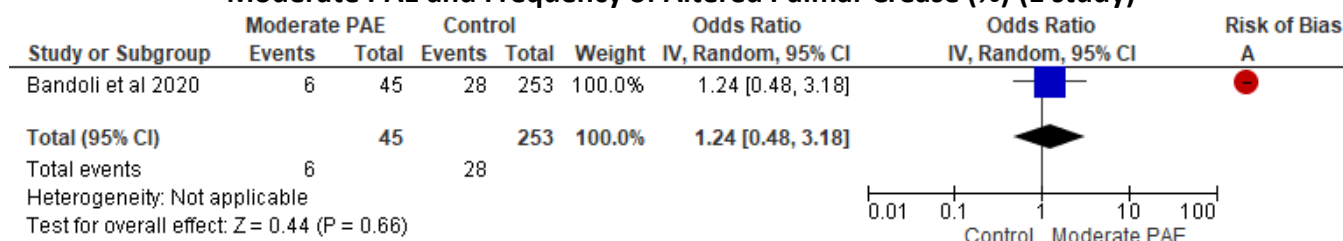
(A) Overall RoB

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

Altered Palmar Crease (%)

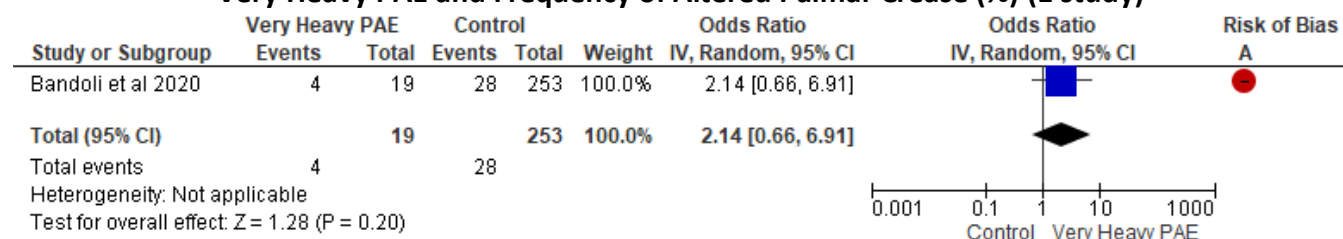
Moderate PAE and Frequency of Altered Palmar Crease (%) (1 study)



Risk of bias legend

(A) Overall RoB

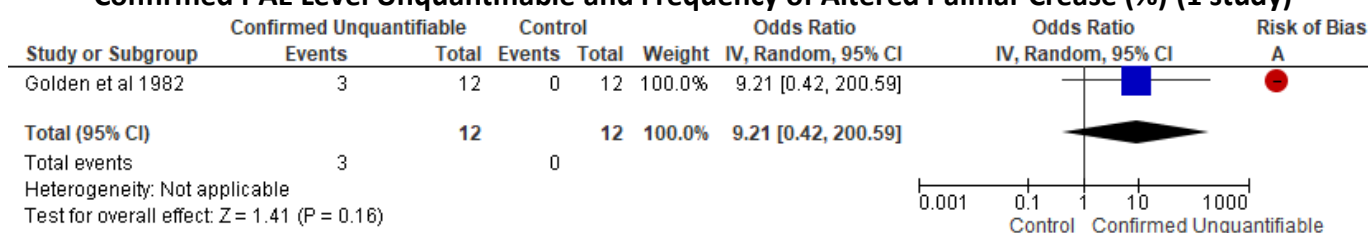
Very Heavy PAE and Frequency of Altered Palmar Crease (%) (1 study)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

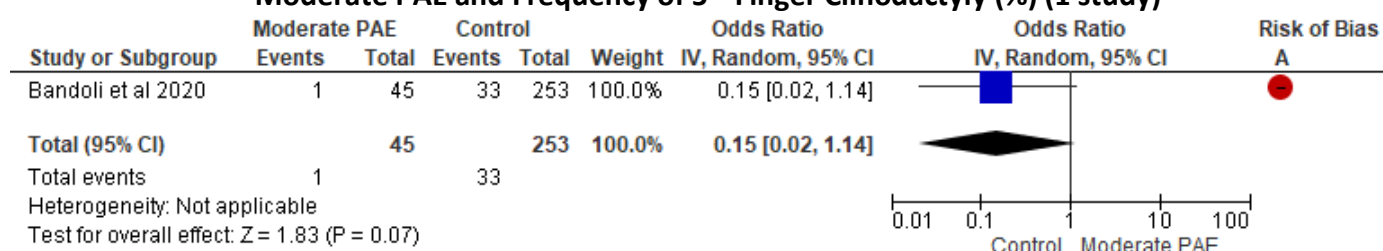
(A) Overall RoB

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

5th FINGER CLINODACTYLY

5th Finger Clinodactyly (%)

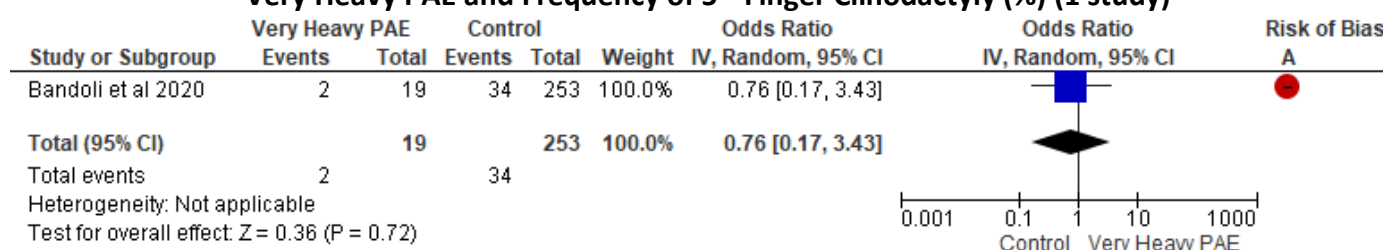
Moderate PAE and Frequency of 5th Finger Clinodactyly (%) (1 study)



Risk of bias legend

(A) Overall RoB

Very Heavy PAE and Frequency of 5th Finger Clinodactyly (%) (1 study)



Risk of bias legend

(A) Overall RoB

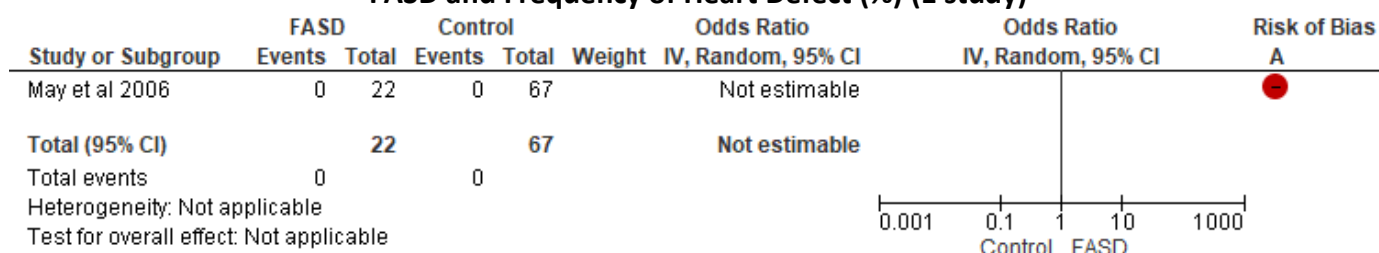
Notes: Bandoli et al 2020 reports 5 trajectories, used trajectory D for moderate (90g/week) and trajectory E (313g/week) for very heavy PAE.

Diagnosed Studies

HEART PROBLEMS

Heart Defect (%)

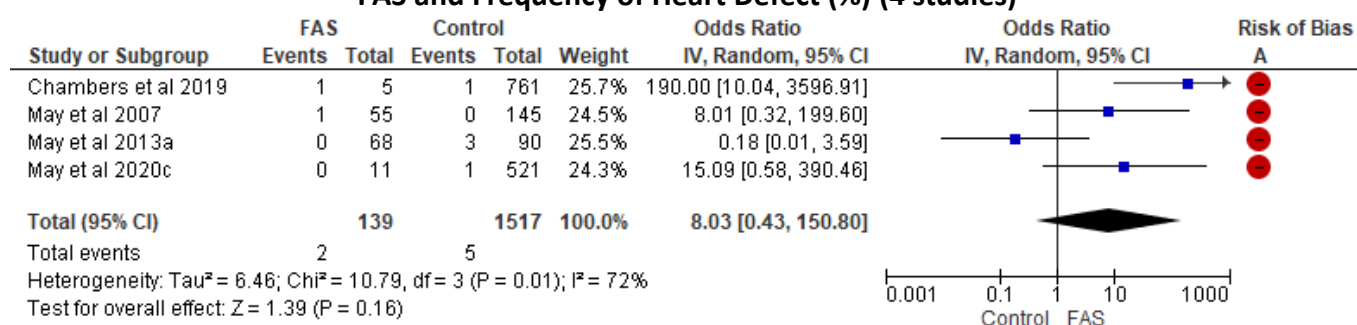
FASD and Frequency of Heart Defect (%) (1 study)



Risk of bias legend

(A) Overall RoB

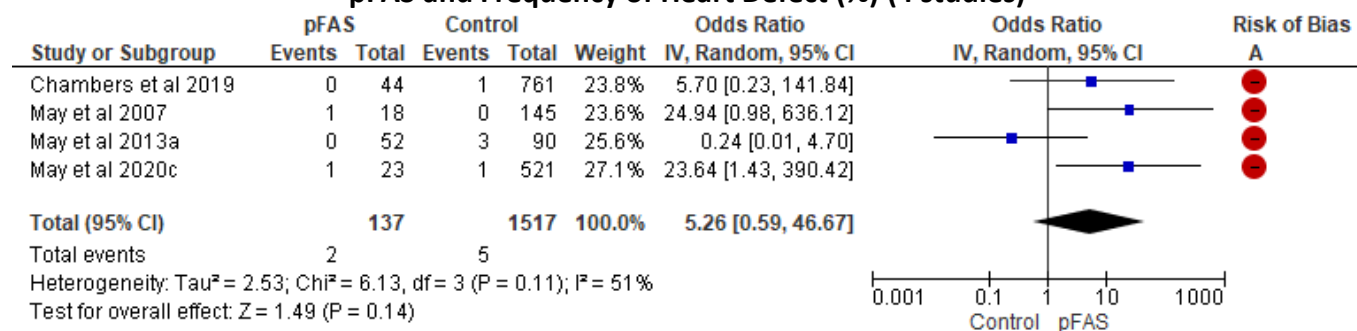
FAS and Frequency of Heart Defect (%) (4 studies)



Risk of bias legend

(A) Overall RoB

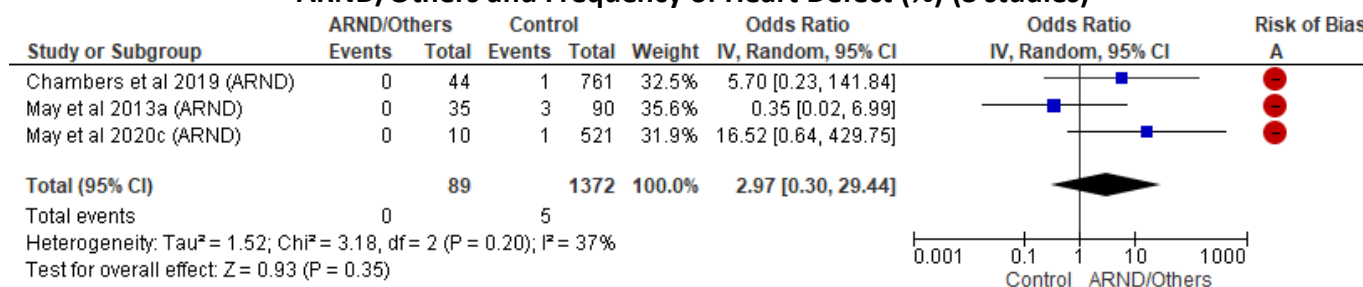
pFAS and Frequency of Heart Defect (%) (4 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Frequency of Heart Defect (%) (3 studies)



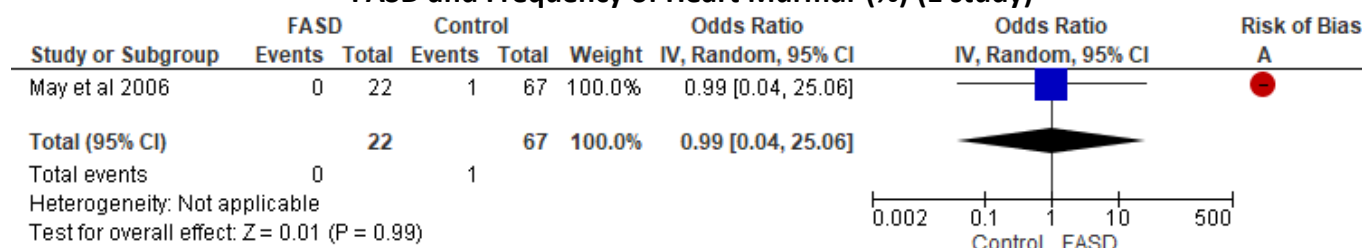
Risk of bias legend

(A) Overall RoB

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

Heart Murmur (%)

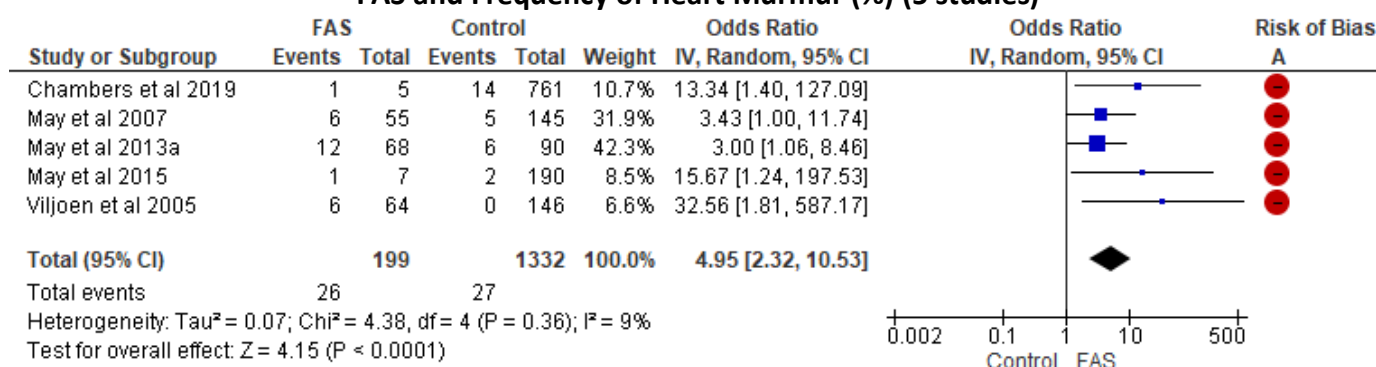
FASD and Frequency of Heart Murmur (%) (1 study)



Risk of bias legend

(A) Overall RoB

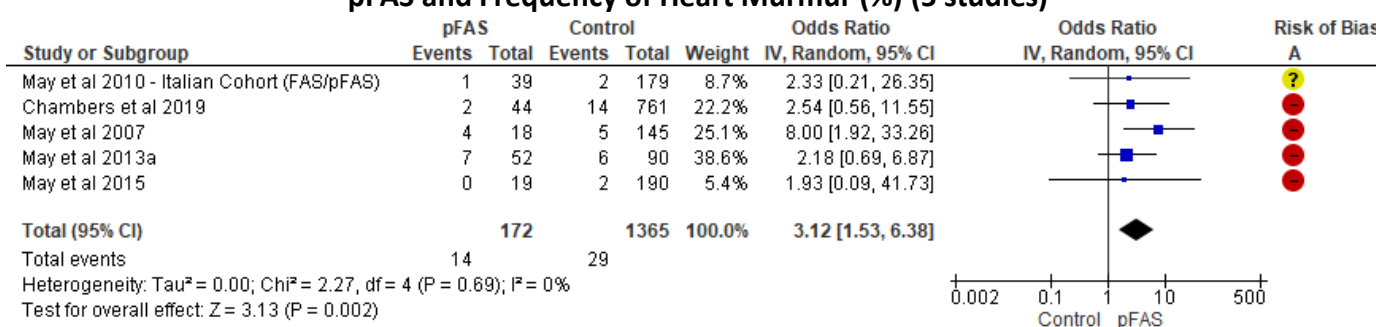
FAS and Frequency of Heart Murmur (%) (5 studies)



Risk of bias legend

(A) Overall RoB

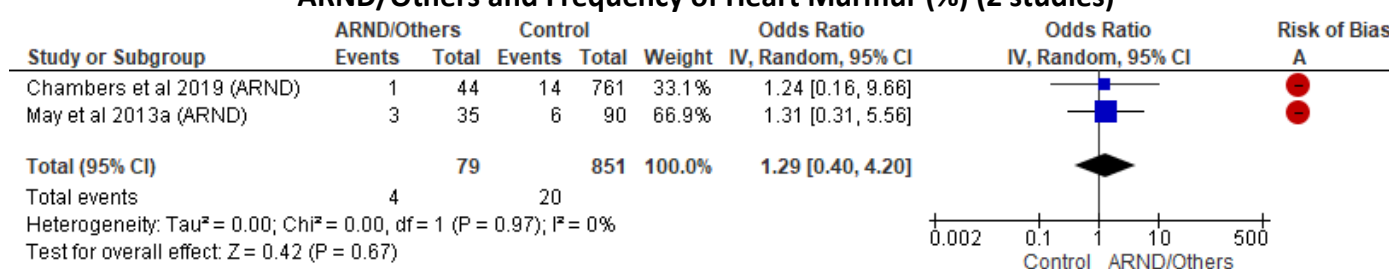
pFAS and Frequency of Heart Murmur (%) (5 studies)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

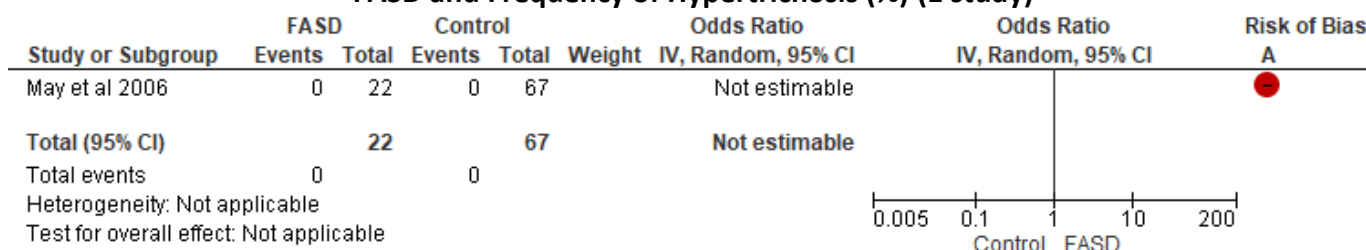
(A) Overall RoB

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

HYPERTRICHOSIS

Hypertrichosis (%)

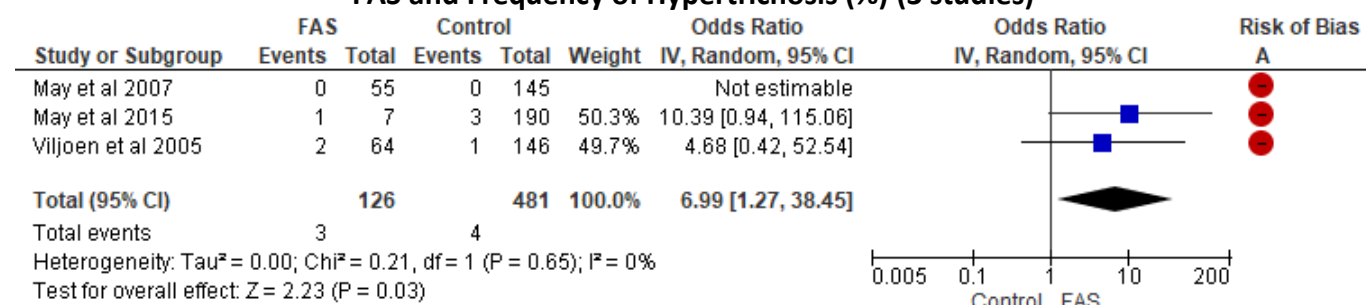
FASD and Frequency of Hypertrichosis (%) (1 study)



Risk of bias legend

(A) Overall RoB

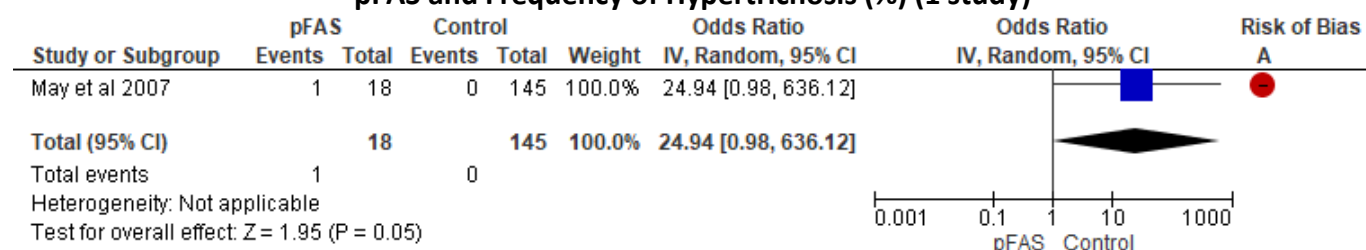
FAS and Frequency of Hypertrichosis (%) (3 studies)



Risk of bias legend

(A) Overall RoB

pFAS and Frequency of Hypertrichosis (%) (1 study)



Risk of bias legend

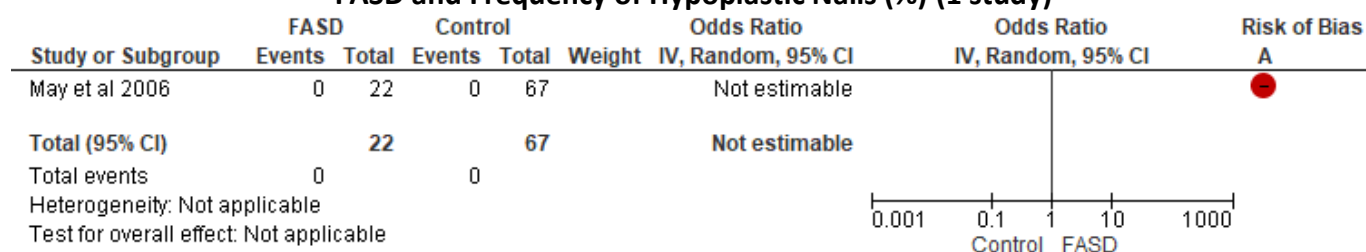
(A) Overall RoB

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

HYPOPLASTIC NAILS

Hypoplastic Nails (%)

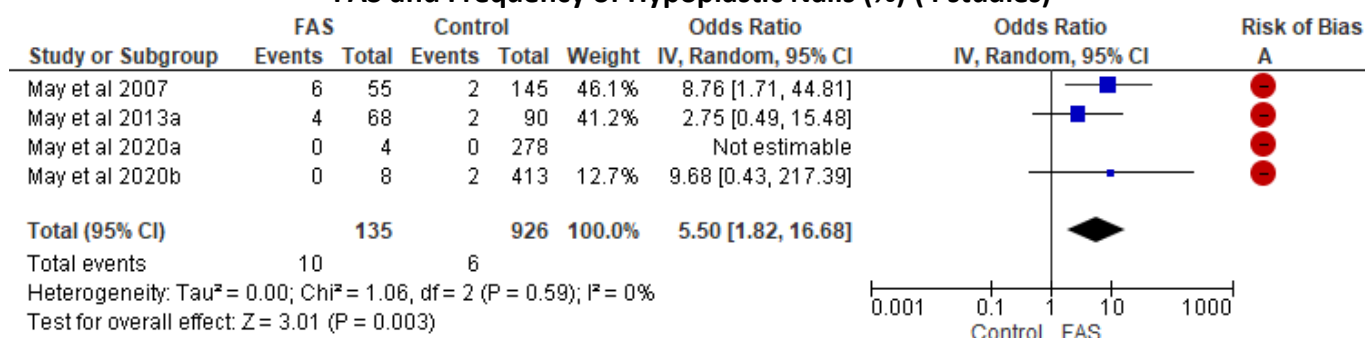
FASD and Frequency of Hypoplastic Nails (%) (1 study)



Risk of bias legend

(A) Overall RoB

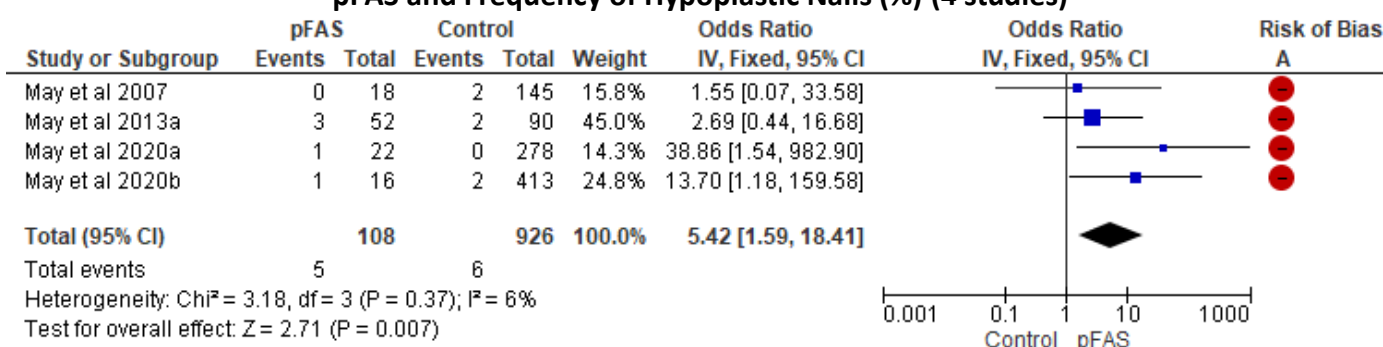
FAS and Frequency of Hypoplastic Nails (%) (4 studies)



Risk of bias legend

(A) Overall RoB

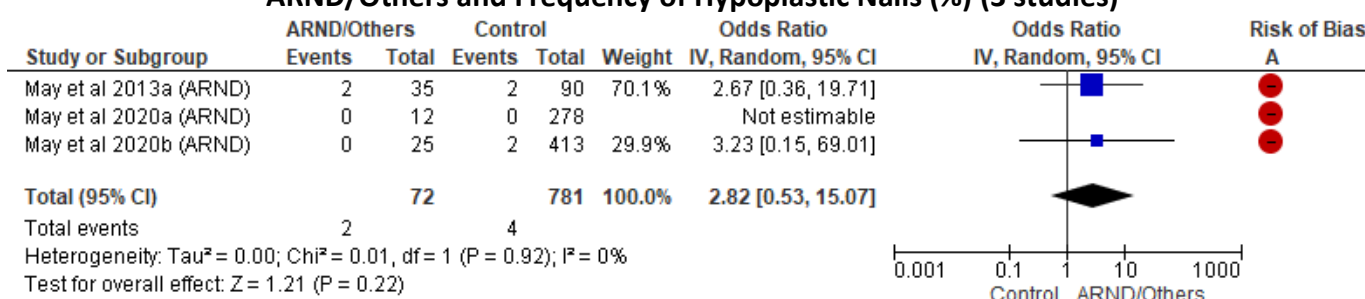
pFAS and Frequency of Hypoplastic Nails (%) (4 studies)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

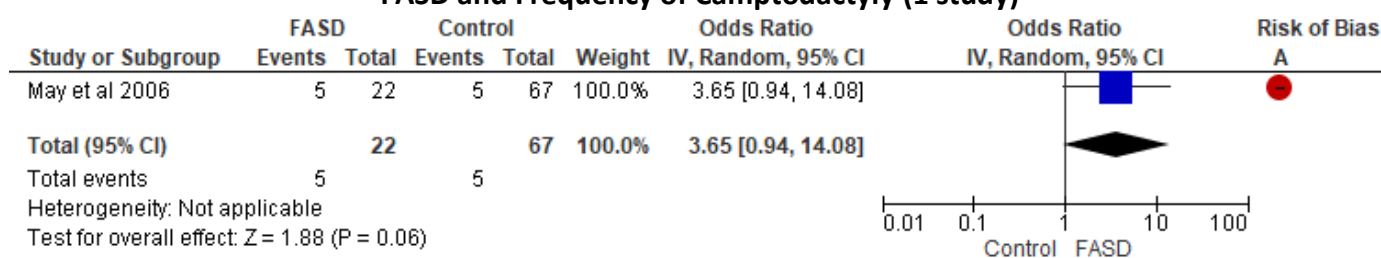
(A) Overall RoB

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

CAMPTODACTYL

Camptodactyly (%)

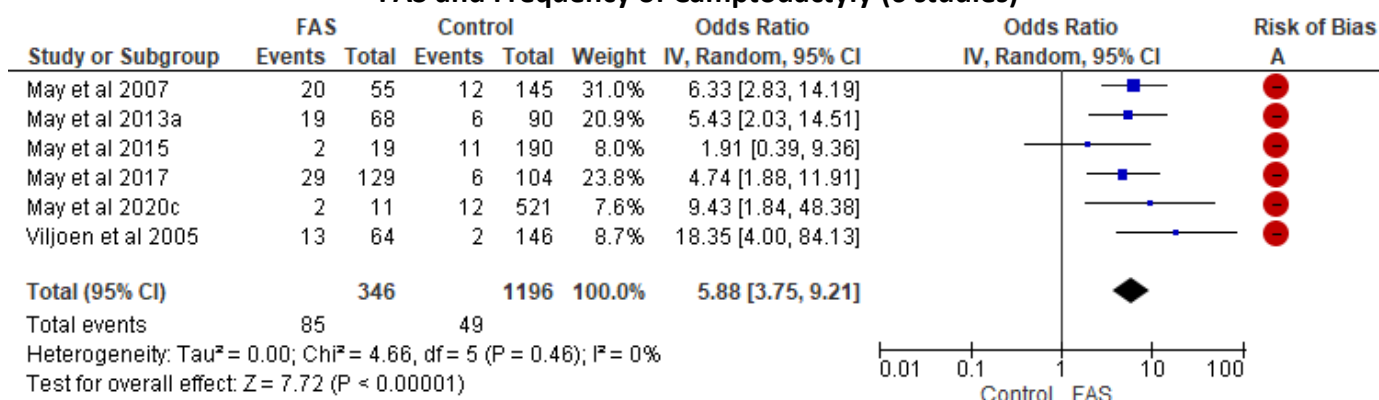
FASD and Frequency of Camptodactyly (1 study)



Risk of bias legend

(A) Overall RoB

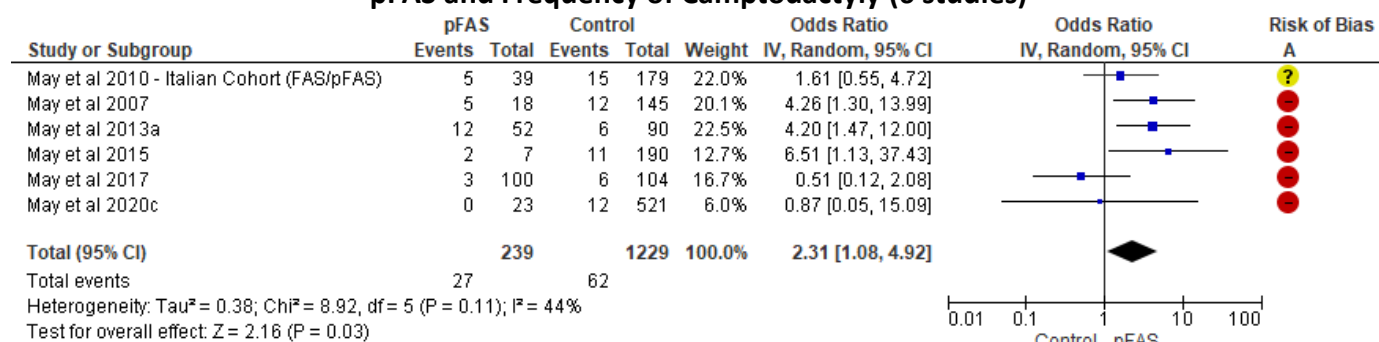
FAS and Frequency of Camptodactyly (6 studies)



Risk of bias legend

(A) Overall RoB

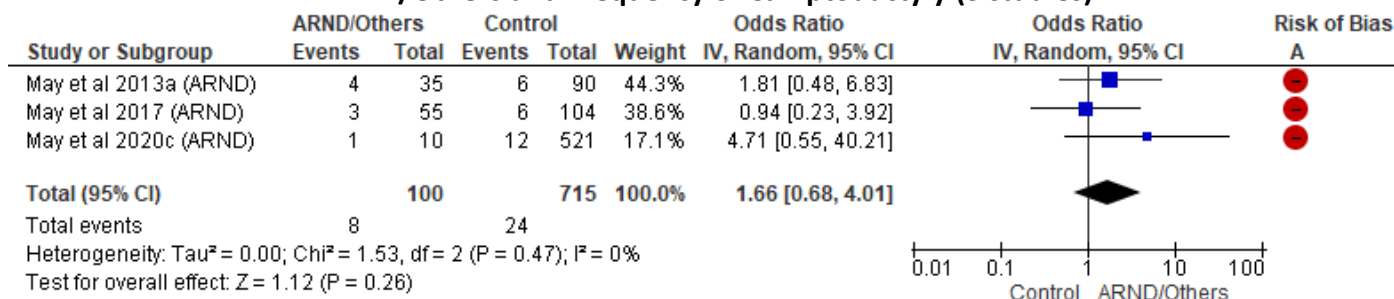
pFAS and Frequency of Camptodactyly (6 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Frequency of Camptodactyly (3 studies)



Risk of bias legend

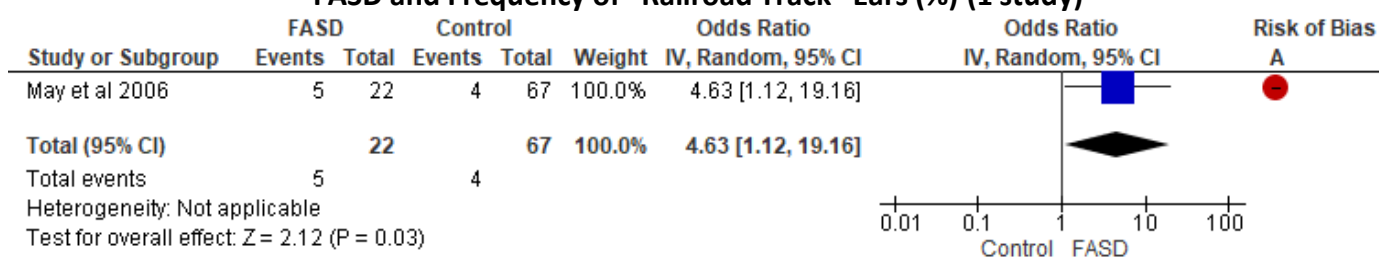
(A) Overall RoB

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

"RAILROAD TRACK" EARS

"Railroad Track" Ears (%)

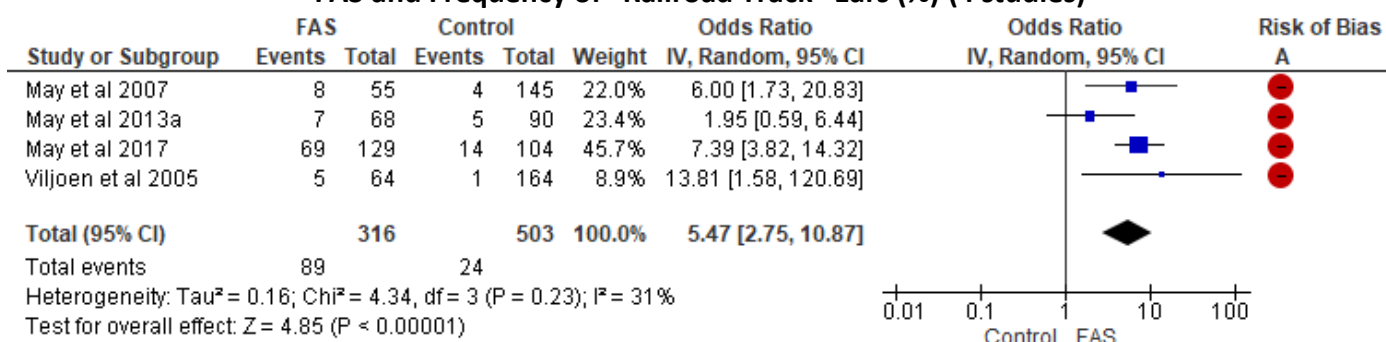
FASD and Frequency of "Railroad Track" Ears (%) (1 study)



Risk of bias legend

(A) Overall RoB

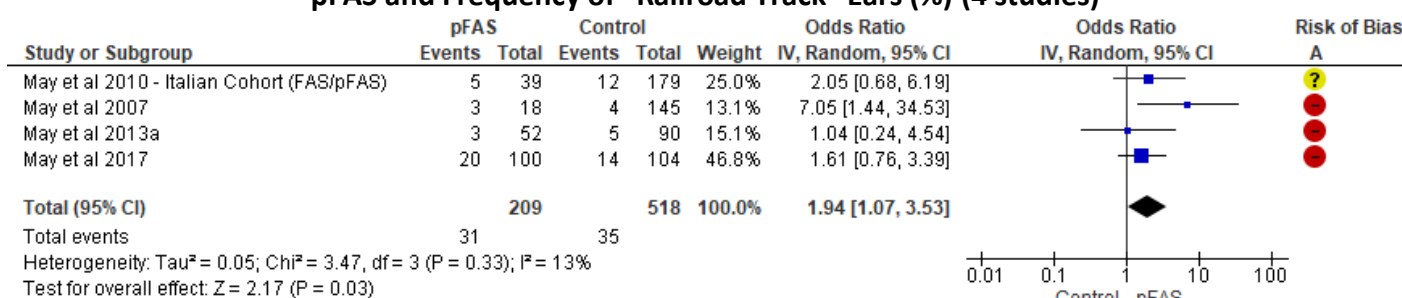
FAS and Frequency of “Railroad Track” Ears (%) (4 studies)



Risk of bias legend

(A) Overall RoB

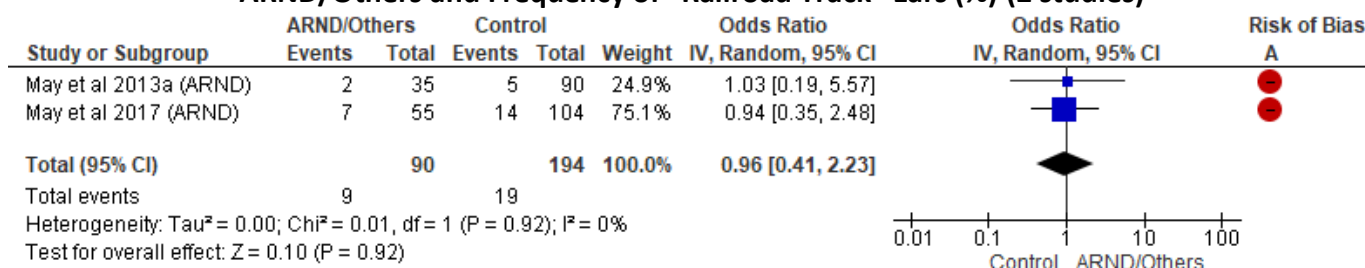
pFAS and Frequency of “Railroad Track” Ears (%) (4 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Frequency of “Railroad Track” Ears (%) (2 studies)



Risk of bias legend

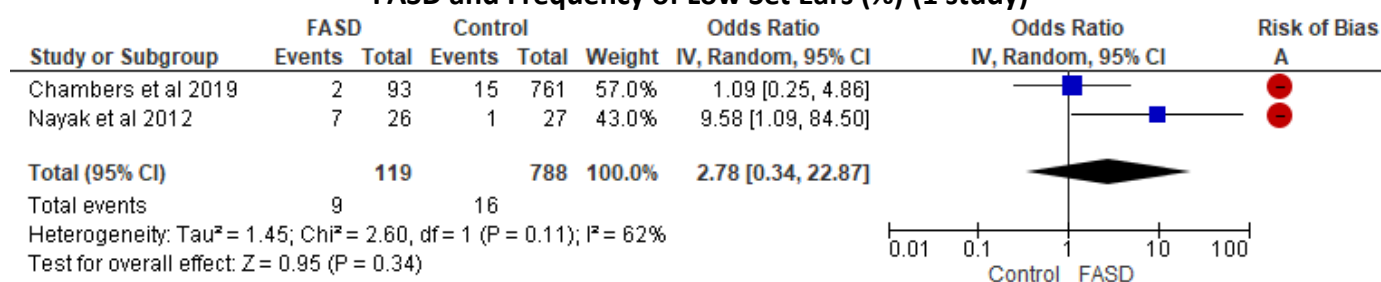
(A) Overall RoB

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 Ears (%) (1 study)



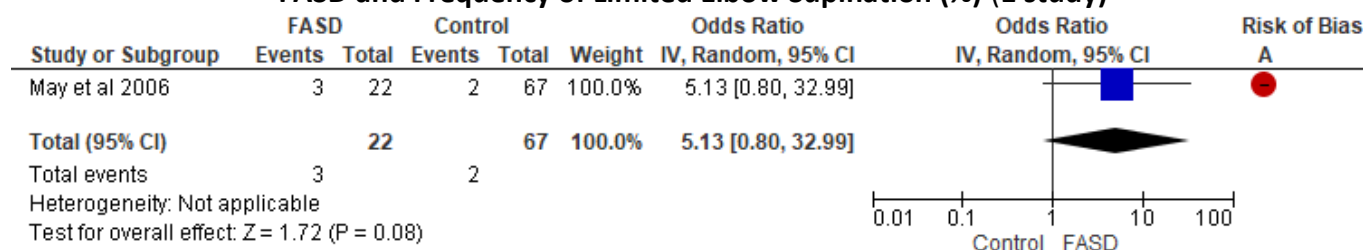
Risk of bias legend

(A) Overall RoB

DECREASED JOINT SUPINATION

Limited Elbow Supination (%)

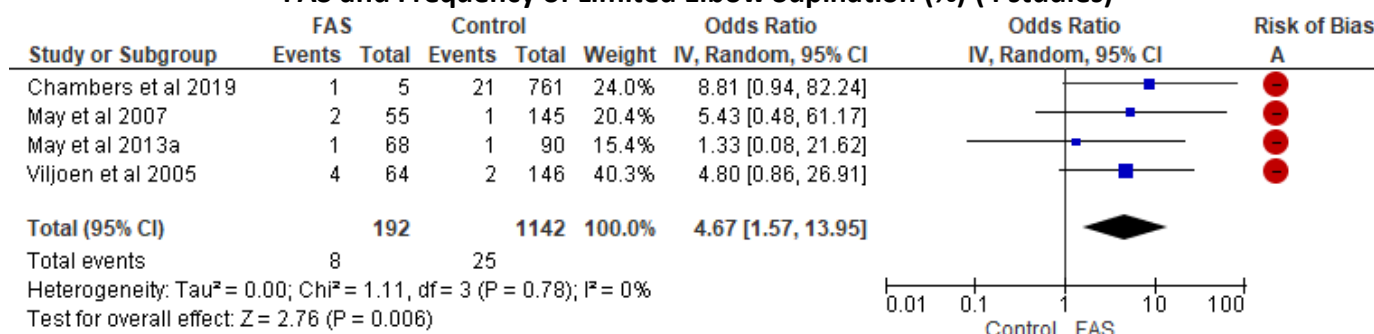
FASD and Frequency of Limited Elbow Supination (%) (1 study)



Risk of bias legend

(A) Overall RoB

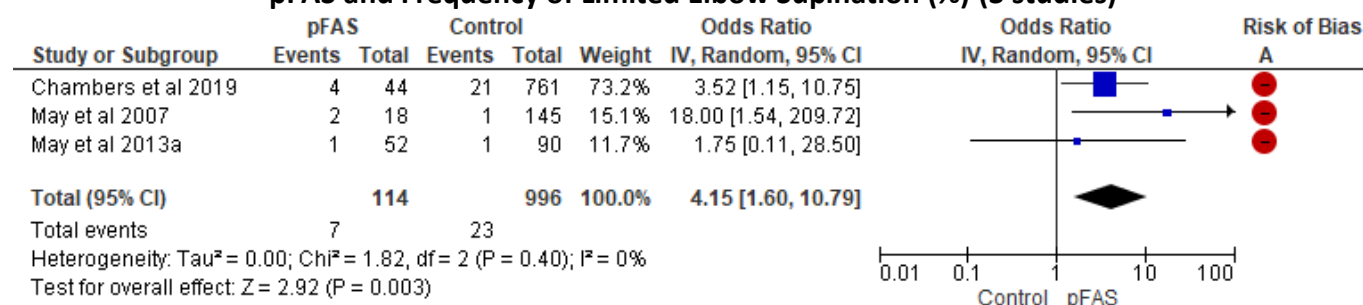
FAS and Frequency of Limited Elbow Supination (%) (4 studies)



Risk of bias legend

(A) Overall RoB

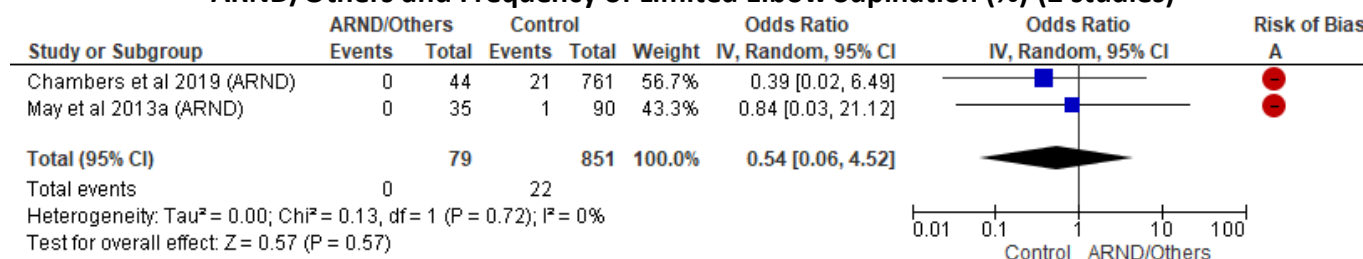
pFAS and Frequency of Limited Elbow Supination (%) (3 studies)



Risk of bias legend

(A) Overall RoB

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



Risk of bias legend

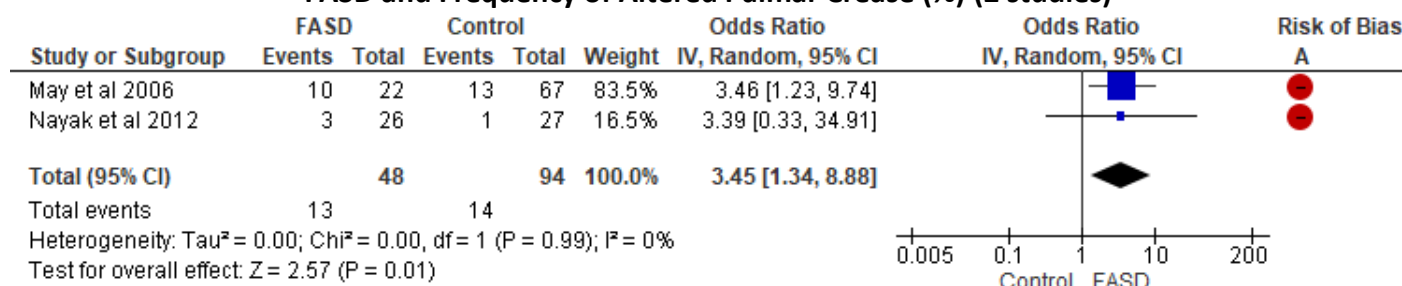
(A) Overall RoB

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

ALTERED PALMAR CREASE

Altered Palmar Crease (%)

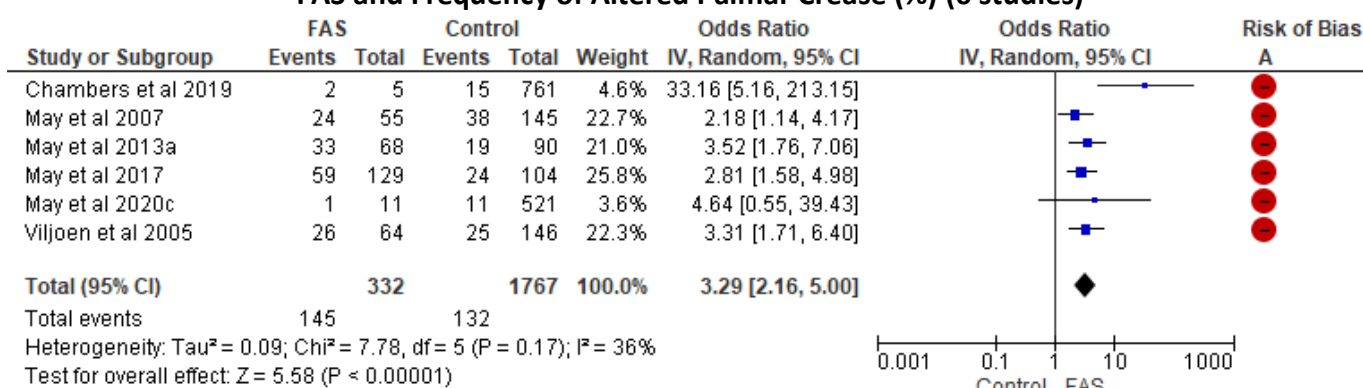
FASD and Frequency of Altered Palmar Crease (%) (2 studies)



Risk of bias legend

(A) Overall RoB

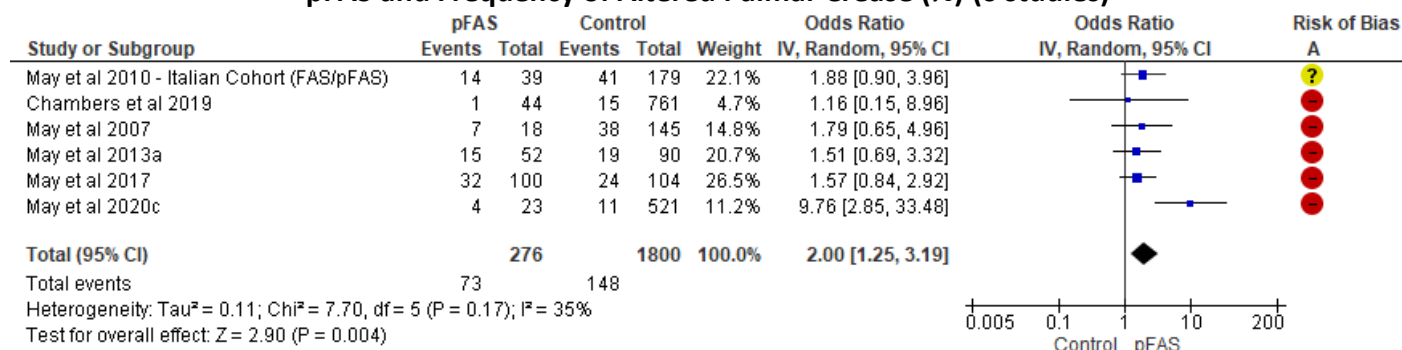
FAS and Frequency of Altered Palmar Crease (%) (6 studies)



Risk of bias legend

(A) Overall RoB

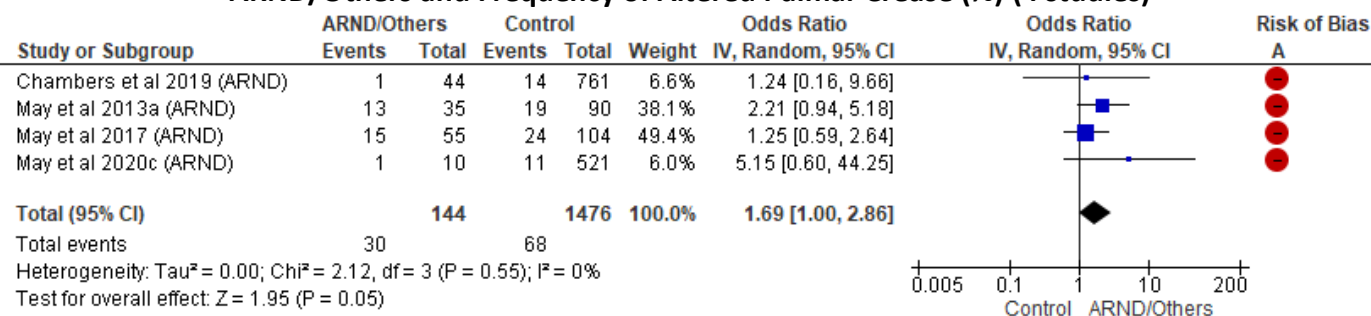
pFAS and Frequency of Altered Palmar Crease (%) (6 studies)



Risk of bias legend

(A) Overall RoB

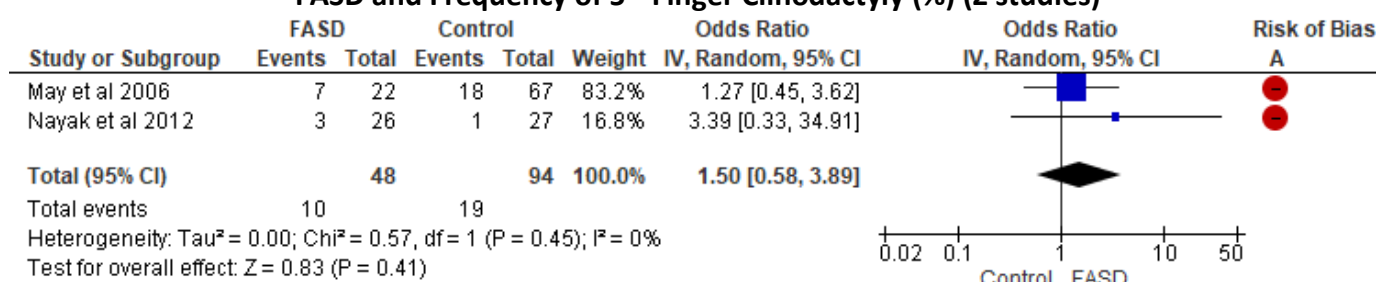
ARND/Others and Frequency of Altered Palmar Crease (%) (4 studies)



Risk of bias legend

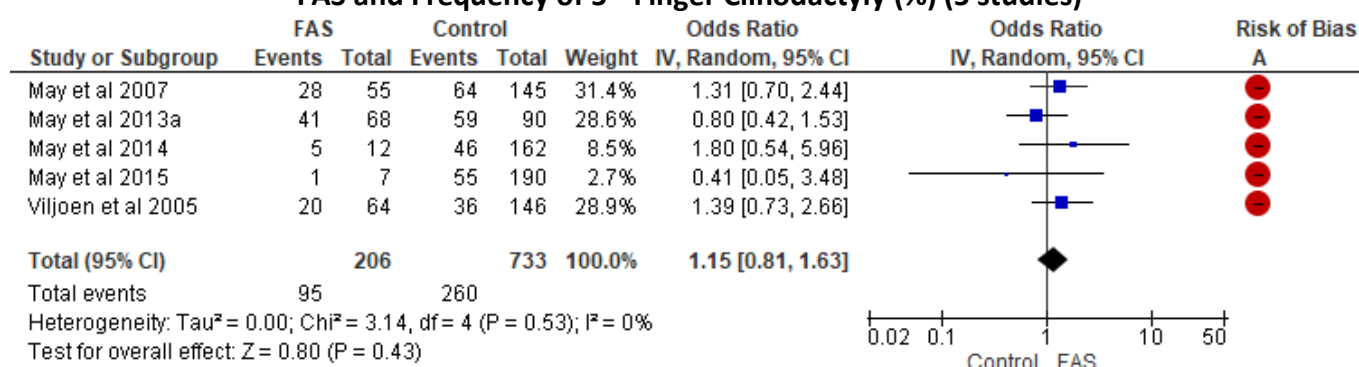
(A) Overall RoB

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.

5th FINGER CLINODACTYLY5th Finger Clinodactyly (%)FASD and Frequency of 5th Finger Clinodactyly (%) (2 studies)

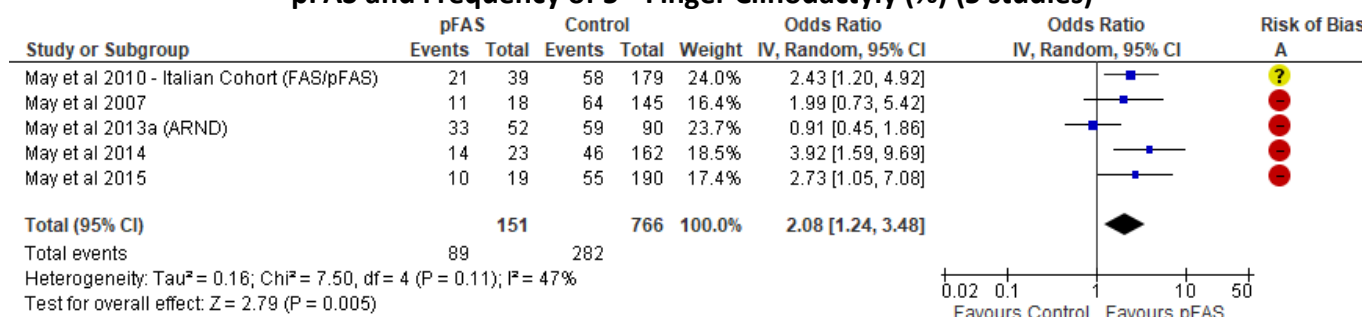
Risk of bias legend

(A) Overall RoB

FAS and Frequency of 5th Finger Clinodactyly (%) (5 studies)

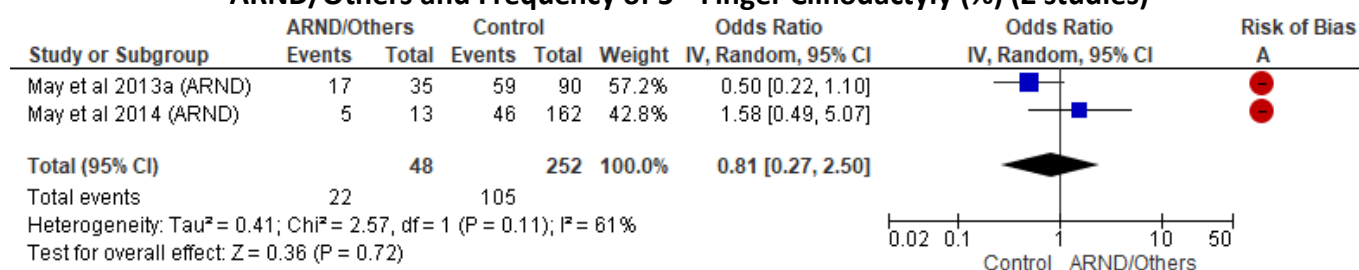
Risk of bias legend

(A) Overall RoB

pFAS and Frequency of 5th Finger Clinodactyly (%) (5 studies)

Risk of bias legend

(A) Overall RoB

ARND/Others and Frequency of 5th Finger Clinodactyly (%) (2 studies)

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 2013a also reports non-syndromal.

Summary of available outcomes for dysmorphology checklist

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

GRADE ratings for dysmorphology checklist

	Certainty assessment					No of patients		Effect		Certainty
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PAE	Control	Relative (95% CI)	Absolute (95% CI)	
EXPOSURE STUDIES										
Dysmorphology Score (m/SD)										
Moderate PAE										
1	serious ^a	not serious	not serious	serious ^{e,f}	none	45	253	-	SMD 0.8 higher (0.47 higher to 1.12 higher)	⊕⊕○○ Low
Very Heavy PAE										
2	serious ^a	not serious	not serious	serious ^{e,f}	none	44	274	-	SMD 1.22 higher (0.75 higher to 1.69 higher)	⊕⊕○○ Low
DIAGNOSED STUDIES										
Dysmorphology Score										
FASD										
3	serious ^a	serious ^b	not serious	serious ^{e,f}	none	89	183	-	SMD 2.18 higher (1.22 higher to 3.14 higher)	⊕○○○ Very Low
FAS										
8	serious ^a	serious ^b	not serious	serious ^e	none	333	1841	-	SMD 2.83 higher (2.14 higher to 3.53 higher)	⊕○○○ Very Low
pFAS										
8	serious ^a	serious ^b	not serious	serious ^e	none	245	1846	-	SMD 2.07 higher (1.70 higher to 2.43 higher)	⊕○○○ Very Low
ARND/Others										
4	serious ^a	serious ^b	not serious	serious ^e	none	195	1310	-	SMD 0.43 higher (0.12 higher to 0.74 higher)	⊕○○○ Very Low

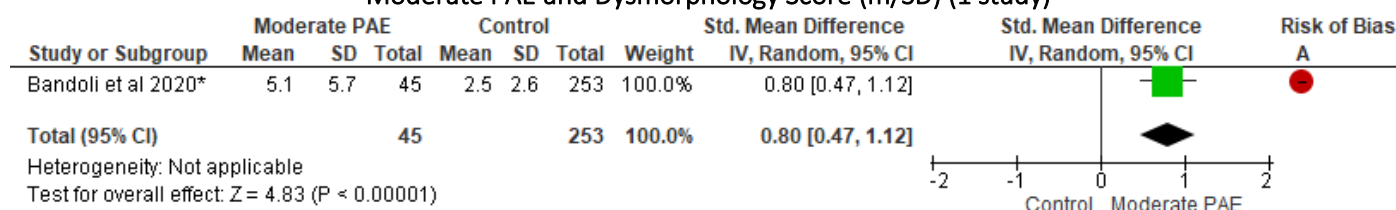
Notes: CI: confidence interval; MD: mean difference; SMD: standard mean difference; OR: odds ratio.

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

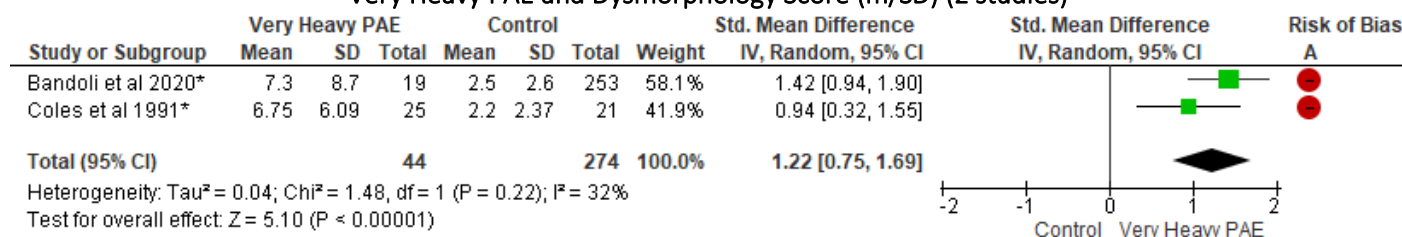
Moderate PAE and Dysmorphology Score (m/SD) (1 study)



Risk of bias legend

(A) Overall RoB

Very Heavy PAE and Dysmorphology Score (m/SD) (2 studies)



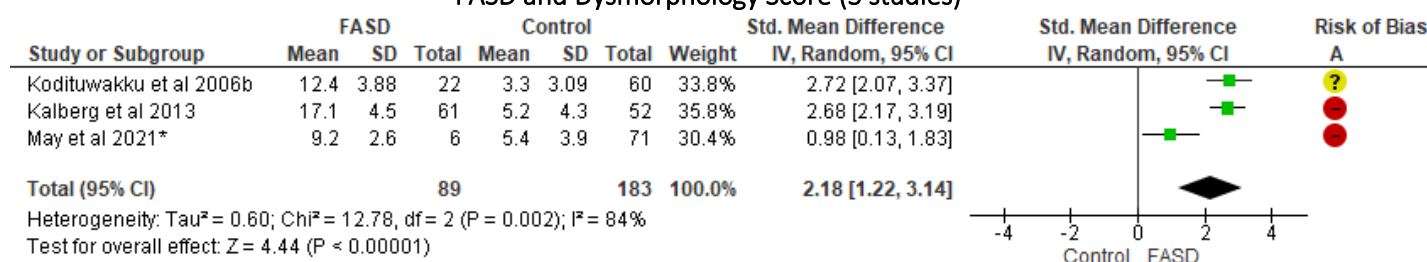
Risk of bias legend

(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

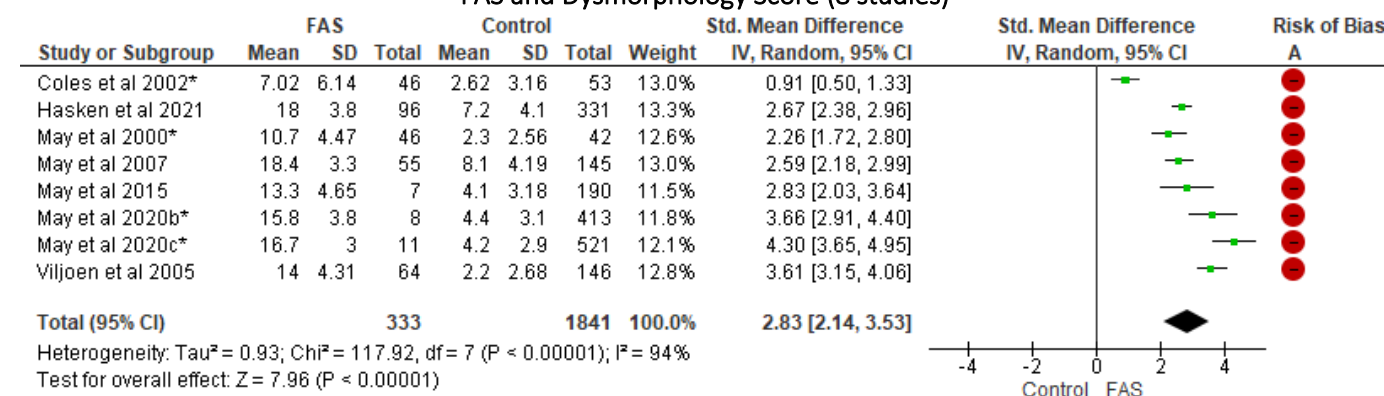
FASD and Dysmorphology Score (3 studies)



Risk of bias legend

(A) Overall RoB

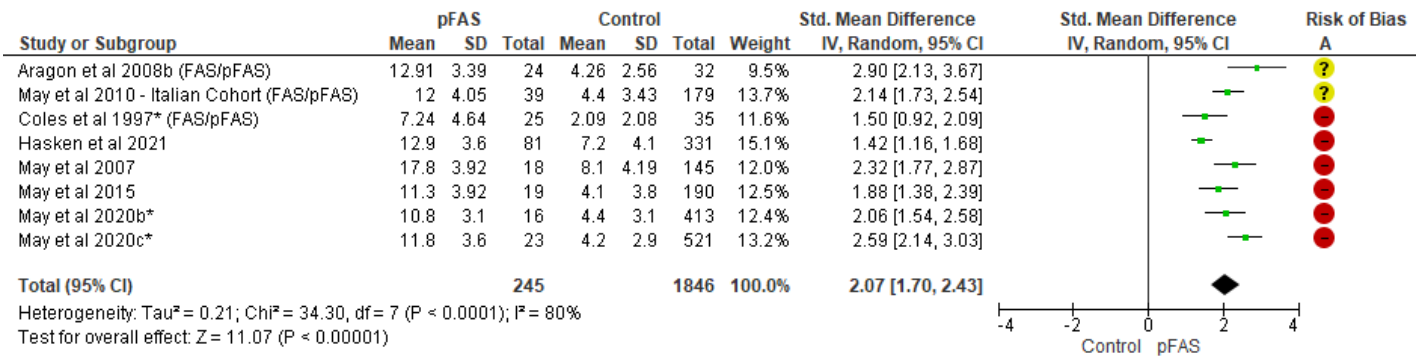
FAS and Dysmorphology Score (8 studies)



Risk of bias legend

(A) Overall RoB

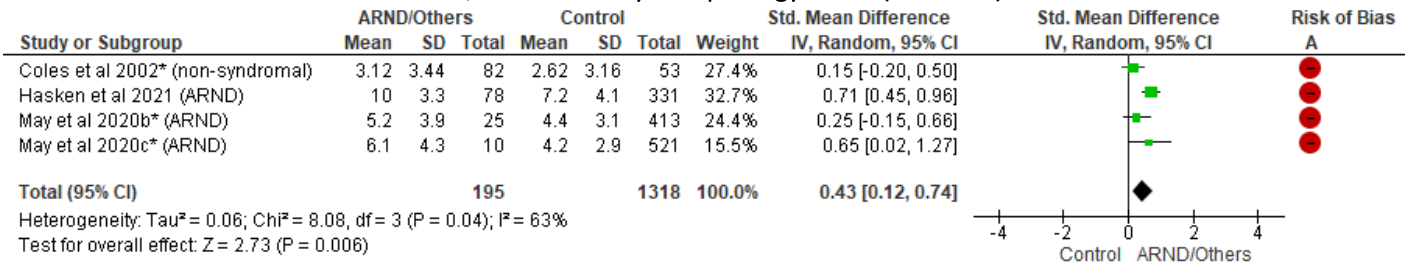
pFAS and Dysmorphology Score (8 studies)



Risk of bias legend

(A) Overall RoB

ARND/Others and Dysmorphology Score (6 studies)



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.