**APRIL 2025** 

# Australian Guidelines for Assessment and Diagnosis of Fetal Alcohol Spectrum Disorder

ASSOCIATION BETWEEN PRENATAL ALCOHOL EXPOSURE PHYSICAL SIZE, DYSMORPHOLOGY AND NEURODEVELOPMENT: SYSTEMATIC REVIEW REPORT

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Funding:	Funding (\$600,000) was provided by the Commonwealth Department of Health to a consortium of 11 organisations: The University of Queensland, Gold Coast Hospital and Health Service, University of Sydney, Telethon Kids Institute, La Trobe University, Griffith University, Patches Paediatrics, West Moreton Hospital and Health Service, NOFASD, FASD Collaboration for assessment and care research and education Incorporated, and Monash Children's Hospital (GO2647).
Photos:	The photos included on the title page were curated and purchased from Jacob Dedman, Digital Journey Photography <u>https://digitaljourneyphotography.com/</u>
Documentation access:	These guidelines and related documents can be found online at: website link <u>https://child-health-</u> <u>research.centre.uq.edu.au/australian-guidelines-assessment-and-</u> <u>diagnosis-fetal-alcohol-spectrum-disorder</u>

## Peer reviewed publication

Citation for the published version of the findings of this review:

Akison LK\*, Hayes N\*, Vanderpeet C, Logan J, Munn Z, Middleton P, Moritz KM, Reid N and the Australian FASD Guidelines Development Group, on behalf of the Australian FASD Guidelines Consortium (2024) Prenatal alcohol exposure and associations with physical size, dysmorphology and neurodevelopment: A systematic review and meta-analysis. BMC Medicine.

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# Authors and contributions

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## **Declarations of interest**

All authors declare they have no personal, financial, or professional interests that could be interpreted to have influenced conduct or results of this systematic review.

# Summary

### What is the problem?

Internationally there is no agreed set of diagnostic criteria for fetal alcohol spectrum disorder (FASD). There is also no comprehensive evidence synthesis available to inform decision-making regarding the clinical features to include in diagnostic criteria for FASD.

### What is the importance?

This systematic review has examined all available outcomes across the variable diagnostic domains for FASD (i.e., physical size, dysmorphology and neurodevelopment) and quantitatively examined their association with prenatal alcohol exposure (PAE) and/or diagnosed FASD. Where specific PAE levels were reported, this has been standardised across studies, allowing for meta-analysis and comparison of outcomes.

### What evidence was found?

306 studies published from 1980 to 2023 were included in this systematic review. There were 106 studies examining physical size across 14 different outcomes that spanned birth to adulthood. Major facial dysmorphology (i.e., of the philtrum, vermilion, and palpebral fissures) was assessed in 43 studies and 32 studies examined minor dysmorphology of other facial and non-facial features. Functional neurodevelopmental outcomes were reported in 195 studies and 110 studies examined structural or neurological outcomes.

For physical size, there was a negative association found between heavy, very heavy, and confirmed but unquantified levels of PAE, although the quality of the evidence ranged from very low to moderate certainty of this association. For major dysmorphology, there was a positive association found between moderate, heavy, and confirmed but unquantified levels of PAE, although there was very low to low certainty of the evidence for this association. For functional neurodevelopmental outcomes there was an association found between heavy, very heavy and confirmed unquantified levels of PAE, with very low to moderate certainty of the evidence for this association. For structural and neurological neurodevelopmental outcomes, there was an association found between all available levels of PAE, with very low to moderate certainty.

#### What were the conclusions?

Associations between PAE and diagnostic outcomes were more consistently observed at heavy and very heavy PAE levels (including confirmed unquantified studies), with less common associations observed at moderate and light PAE levels.

## 1. Background and rationale

In 2016, the first Australian Guide to Diagnosis of FASD was published in Australia (Bower & Elliott, 2016) to support a consistent approach to assessment and diagnosis of FASD nationally. Consistent with the need to review and update clinical practice guidance, the Commonwealth Department of Health funded a consortium of 11 organisations to review, update and disseminate guidelines for assessment and diagnosis of FASD. A major challenge in developing these clinical practice guidelines is that, internationally, there is no agreed upon set of diagnostic criteria for FASD. Currently, there are over 10 different diagnostic criteria in use in specialist diagnostic clinics around the world, with many clinicians reporting use of multiple diagnostic criteria in practice (Reid et al., 2022). Consequently, the current review focused on examining all the available evidence regarding the association between prenatal alcohol exposure and the specific outcomes that are considered across available diagnostic criteria to help inform decision-making regarding the clinical features to include when diagnosing FASD.

## 2. Objective and review question

The objective was to systematically identify and analyse the existing published evidence for an association between PAE or FASD with diagnostic outcomes across the domains of physical size, dysmorphology, and neurodevelopment.

#### **Review Question**

What is the available evidence for each component of the diagnostic criteria for FASD (i.e., prenatal alcohol exposure, physical size, dysmorphology, and neurodevelopment)? See **Table 1** for details of the population, exposure, comparator, and outcomes considered for this research question.

PECO <sup>1</sup> Component	Definition/Eligibility for inclusion
<u>P</u> opulation	Pregnant women/people and their offspring (of any age).
	• Studies conducted with participants living in any country, and from all settings were eligible.
<u>E</u> xposure	<ul> <li>Eligible studies were those examining prenatal alcohol exposure (PAE) and/or FASD diagnosis.</li> <li>Studies were eligible if they included information about PAE or diagnostic criteria used. We anticipated that these methods would vary across studies. To account for differences in the methods used to measure PAE, data were extracted on measurement methods and potential biases and subsequent confounding assessed.</li> </ul>
<u>C</u> omparator	<ul> <li>Studies examining prenatal alcohol exposure:</li> <li>Non-exposed control groups – could include abstainers 'never drinkers' or 'not drinking during pregnancy.'</li> <li>Comparison groups that included some (or all women) who had consumed 'very little' or 'minimal' PAE were included, but this level must have been less than 10 grams of alcohol per week.</li> <li>Studies examining individuals diagnosed with FASD:</li> <li>Typically developing controls.</li> <li>Individuals with 'minimal' PAE were included in the comparison groups, but this level must have been less than 10 grams of alcohol per week.</li> </ul>
<u>O</u> utcome	<u>Physical Size</u> : Eligible studies were those examining physical size outcomes in individuals with PAE or diagnosed FASD. Studies were eligible irrespective of data collection methods. Physical size outcomes of interest included: birth weight (in grams and percentiles), birth length (in centimetres and percentiles), small for gestational age (<10 <sup>th</sup> percentile), low birth weight (<2500 g), postnatal weight (in kilograms and percentiles), postnatal height (in centimetres and

#### Table 1. Population, Exposure, Comparator and Outcome (PECO) Components

percentiles), restricted postnatal weight (<10 <sup>th</sup> or <3 <sup>rd</sup> percentile) and restricted postnatal
<ul> <li><u>Dysmorphology</u>: Eligible studies were those examining dysmorphic features in individuals with PAE or diagnosed FASD. Studies were eligible irrespective of assessment methods. Dysmorphic features of interest included the 3 sentinel facial features typically used in the diagnosis of fetal alcohol syndrome (FAS) (philtrum, vermilion, and palpebral fissures), the 18 minor facial and non-facial features listed on the Hoyme 2016 dysmorphology checklist (Hoyme et al</li> </ul>
<ul> <li>and non-facial features listed on the Hoyme 2016 dysmorphology checklist (Hoyme et al., 2016), and the maxillary and mandibular arcs (Abell et al., 2016).</li> <li><u>Neurodevelopment:</u> Eligible studies were those examining structural and/or functional neurodevelopmental outcomes either through direct measures or questionnaires. Structural outcomes included measures of head circumference (in centimetres or percentiles); clinical or quantitative MRI measures; or incidence of seizures, cerebral palsy, visual impairment, or hearing loss. Functional outcomes included motor, language, intelligence, academic,</li> </ul>
behaviour, attention, social, executive function, adaptive behaviour, memory, working memory, sensory processing, or soft neurological signs.

Note: <sup>1</sup> Adapted from PEO, as described in Munn et al. (2018).

# 3. Methods

## 3.1 Protocol and registration

A systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; <u>https://www.crd.york.ac.uk/prospero/CRD42021230522</u>). The review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; (PRISMA; Page et al., 2021).

## 3.2 Study inclusion and exclusion criteria

## 3.2.1 Inclusion criteria

Criteria for inclusion in the review included studies published in English that were case-control or cohort designs and presented data that examined the association between PAE (exposure studies) or FASD (diagnosed studies) and one or more outcomes as per **Tables 2-5**. Results include further specific details regarding the grouping of the functional neurodevelopmental outcomes. These groupings were determined in consultation with the Guidelines Development Group.

Outcome Domain	Measures
Birth weight	Small for gestational age (SGA, majority of studies defined as <10 <sup>th</sup>
	percentile)
	Low birth weight (LBW, majority of studies defined as <2500 g)
	Birth weight (g)
	Birth weight percentiles
Birth length	Birth length (cm)
	Birth length percentile
Postnatal weight (measurement taken	Weight ≤ 10 <sup>th</sup> percentile
any time after birth)	Weight percentiles
	Weight (kg) ≤ 12 months of age (exposure studies)
	Weight (kg) >12 months (exposure studies)
	Weight (kg) 6-9 years of age (diagnosed studies)
	Weight (kg) 9-18 years of age (diagnosed studies)

#### Table 2. Summary of physical size outcomes

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Postnatal height (measurement taken	Height $\leq 10^{\text{th}}$ percentile
any time after birth)	Height percentiles
	Height ≤12 months of age (exposure studies)
	Height (cm) >12 months of age (exposure studies)
	Height (cm) 6-9 years of age (diagnosed studies)
	Height (cm) 9-18 years of age (diagnosed studies)

# Table 3. Summary of dysmorphology outcomes

Outcome Domain	Measures
Philtrum measures	Frequency of smooth philtrum (rank 3 or 4+) as per lip/philtrum guide (Astley & Clarren, 2000; Hoyme et al., 2016).
	Philtrum length (mm) defined as the length of the vertical groove between the border of the upper lip (vermilion) and the base of the nose.
	Philtrum smoothness (rank 1 to 5) as per lip/philtrum guide (Astley & Clarren, 2000; Hoyme et al., 2016).
	Frequency of long philtrum, as defined by Hoyme et al. (2005) or Hoyme et al. (2016).
	Frequency of hypoplastic philtrum, as defined by Jones et al. (2021).
Vermilion measures	Frequency of thin vermilion (rank 3 or 4+) as per lip/philtrum guide (Astley & Clarren, 2000; Hoyme et al., 2016).
	Vermilion thinness (rank 1 to 5) as per lip/philtrum guide (Astley & Clarren, 2000; Hoyme et al., 2016).
	Frequency of thin upper lip as defined by Jones et al. (1973) and Jones et al. (2021).
Palpebral fissure	Short palpebral fissures (<10 <sup>th</sup> or <3 <sup>rd</sup> percentile). Reported norms defined by Stromland
measures	et al. (1999), Thomas et al. (1987) or Jones et al. (2021) or noted when not reported.
	Palpebral fissure length (mm) defined as the distance between the inner and outer canthi of the eye.
	Palpebral fissure length (centile). Normative charts noted where available.
Minor facial	Face: hypoplastic midface.
dysmorphology (as per checklist reported in	Eyes: strabismus, decreased interpupillary distance ( $\leq 25\%$ ), decreased innercanthal distance ( $\leq 25\%$ ), optosis, or epicanthal folds.
Hoyme et al. (2016)	Nose: anteverted nares/nostrils, or flat nasal bridge.
otherwise)	Mouth and jaw: prognathism; maxillary arc or mandibular arc (Abell et al., 2016).
Minor non-facial	Hair growth: hypertrichosis.
dysmorphology (as per	Ears: 'Railroad Track' ears.
checklist reported in	Cardiac: heart murmur or congenital heart defect.
Hoyme et al. (2016))	Joints: limited/decreased joint supination (e.g., elbow).
	Hands: hypoplastic nails, camptodactyly, 5 <sup>th</sup> finger clinodactyly, or altered palmar crease.
Total Dysmorphology	'Total Dysmorphology Score' as defined by Coles et al. (1985), Stratton et al. (1996),
Score	Coles et al. (1997), Hoyme et al. (2005) or Hoyme et al. (2016).

# Table 4. Summary of neurodevelopmental outcomes

Outcome domain	Measures
IQ/Cognition Included: Full-Scale, Verbal,	Bayley's Scale of Infant Development (BSID, Versions II and III)
	McCarthy Scales of Children's Abilities (MSCA)
Performance and Non-Verbal IQ.	Wechsler Intelligence Scale for Children (WISC, Versions III, IV, V and Revised)
vrs of age) and school-age (4	Wechsler Preschool and Primary Scale of Intelligence (WPPPSI, Revised Version)
yrs+)	Wechsler Adult Intelligence Scale (WAIS)
	Malin's Intelligence Scale for Indian Children (MISIC)
	Wide Range Intelligence Test (WRIT)

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	Kaufman Brief Intelligence Test (K-BIT)
	Kaufman Assessment Battery for Children (K-ABC)
	Differential Ability Scales (DAS, Version II)
	Leiter International Performance Scale (Revised Version)
	Raven's Coloured Progressive Matrices
	Test of Non-Verbal Intelligence (TONI)
	The Test for Reception of Grammar (TROG)
Language	Peabody Picture Vocabulary Test (PPVT, Versions III and Revised)
Included: Data split by age (<3	A Developmental NEuroPSYchological Assessment (NEPSY, Version II)
yrs, 3-5 yrs, >5 yrs). At least one	Subtests: Word Generation, Phonological Processing, and Comprehension of
measure from each study	Instructions
reported. Composite language	Clinical Evaluation of Language Fundamentals (CELE Versions Preschool IV and V
clinically relevant scores	Composite)
prioritised when available.	Bayley's Scales of Infant Development (BSID, Version III)
	Subtest: Language
	Griffith Mental Development Scales (GMDS)
	Subtest: Speech-Hearing
	Pustioni Test of Language Comprehension
	Subtosts: Total Errors and Qualitative
	Coldman Eriston 2 Test of Articulation (CETA 2)
	Subtort: Speech Sound
	Sublest: Speech Sound
	Oral Narrative
	Subtests: Total humber of words and total number of different words
	Lest of Language Competence (TLC)
	Subtest: Figurative Language
	Test of Language Development (TOLD, Version I)
	Subtest: Sentence Combining
	Children's Communication Checklist (CCC, Version 2)
	Subtest: General Language Parent Report
	Ages & Stages Questionnaire
	Subtest: Language Parent Report
	Connors Comprehensive Behaviour Rating Scale (CCBRS)
	Subtest: Language Parent Report
Motor	Bayley's Scales of Infant Development (BSID, Versions II and III)
Included: At least one measure	Subtests: Motor/Psychomotor Index, Gross Motor, and Fine Motor
Composite motor scores (total	Brazelton Neonatal Behavioral Assessment Scale (BNBAS)
motor, gross motor, fine motor),	Subtest: Motor Performance
relevant subdomains, and	Beery Buktenica Developmental Test of Visual Motor Integration (VMI)
clinically relevant scores	Motor Age Test
prioritised when available.	Subtest: Gross Motor
	Griffiths Mental Development Scales (GMDS)
	Subtest: Motor
	Hand Game
	Grooved Pegboard Test and Rolyan 9-Hole Peg Test
	Motor Age Test
	Movement Assessment Battery for Children (MABC)
	Bruininks-Oseretsky Test of Motor Proficiency (BOTMP/BOT, Versions I and II)
	M-FUN Draw-a-Kid
	Clinical Observations of Motor and Postural Skills (COMPS)
Academic	Bracken Basic Concept Scale (BBSC)
Included: Overall academic	Kaufman Assessment Battery for Children (K-ABC)
achievement, reading/ literacy	Wechsler Individual Achievement Test (WIAT, Version II)
and mathematical/numeracy	Wide Range Achievement Test (Versions 3 and Revised)
מטווונוכז.	Woodcock Johnson Quantitative Concepts

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	Woodcock Reading Mastery
	Observational Questionnaire for the Early Identification of Learning Difficulties
	(IPDA Questionnaire – Italian)
	Key Stage 2 (UK National Curriculum Assessment)
	Western Australian Literacy and Numeracy Assessment (WALNA)
Memory	California Verbal Learning Test – Children's Version (CVLT-C)
Included: Composite memory	Subtests: Short Delay Recall and Long Delay Free Recall. List A total trials number
scores (visual, verbal/ auditory,	correct
non-verbal) prioritised when	Kaufman Assessment Battery for Children (K-ABC)
available. Single outcomes	Subtests: Sequential (Short Term Memory)
reported in clinically relevant.	Rev Complex Figure Test and Recognition Trial (RCFT)
	Subtests: 3-min Immediate Recall and 30-min Delayed Recall
	Rev-Osterrieth Complex Figure (ROCE)
	Subtests: Immediate Recall and Delayed Recall
	Bey Auditory Verbal Learning Test (RAV/LT)
	Subtests: Immediate Recall and 20-min recall
	A Developmental NEuroDSVchological Assessment (NEDSV, Version II)
	Subtest: Momeny for Names
	Sublest. Memory of 16 objects
	Wemory of 10 objects
	Subtests: Object Immediate Recail and Object Delayed Recail
	word Stem Completion
	Subtest: Target
	Children's Memory Scale (CMS)
	Subtests: Stories Immediate recall, Stories Delayed Recall, Immediate Recall, and
	Delayed Recall
	Wide Range Assessment of Memory and Learning (WRAML)
	Subtests: Story Memory, Verbal Memory Index, Visual Memory Index
	Nonverbal Selective Reminding Memory Test (NVSRT)
	Subtests: Mean Recall and Delayed Recall
	Verbal Selective Reminding Task (VSRT)
	Subtests: Mean Recall and Delayed Recall
	Test of Memory and Learning (TOMAL)
	Subtests: Immediate Recall and Delayed Recall
	Biber Figure Learning Test (BFLT)
	Subtest: Delayed Recall
	Everyday Memory Questionnaire (EMQ)
	Subtest: Spatial Memory
	CANTAB
	Subtest: Pattern Recognition
Attention	A Developmental NEuroPSYchological Assessment (NEPSY, Versions I and II)
Included: At least one measure	Subtests: Auditory Attention and Response Set
from each study reported.	Test of Everyday Attention for Children (TEA-Ch, Version V)
Composite attention scores,	Subtests: Selective Attention and Sustained Attention
clinically relevant outcomes	Continuous Performance Task (CPT, Version II), Integrated Visual and Auditory (IVA),
prioritised when available.	and VIGIL/W
	Subtests: Total Errors, Omission Errors, and Commission Errors
	Test of Variable Attention (TOVA)
	Subtests: Omission Errors and Commission Errors
	Leiter
	Subtest: Sustained Attention
	D2 Test of Attention
	Subtest: Net Result
	Neurobehavioral Evaluation System (NES: Version III)
	Subtoste: Animale Following Number Correct

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	Child Behaviour Checklist (CBCL), Teacher Report Form (TRF), and Adult Self-report (ASR)
	Subtests: Attention and Inattention
	Disruptive Behaviour Disorder Rating Scales (DBD, Caregiver and Teacher Versions) Subtest: Attention
Executive Function	Behaviour Rating Inventory of Executive Function (BRIEF, Versions Caregiver and
Included: At least one measure from each study reported. Composite scores, relevant subdomains, and clinically relevant outcomes prioritised when available.	Teacher) Subtests: Global Executive Composite, Behavioural Regulation Index, Metacognition Index, Inhibit, Shift, Monitor, Plan/Organise, Working Memory
	A Developmental NEuroPSYchological Assessment (NEPSY, Versions I and II) Subtests: Speeded Naming, Inhibition Naming, Inhibition Switching, Animal Sorting, Letter Fluency, Category Fluency
	Wisconsin Card Sorting Test (WCST)
	Subtests: Composite, Total errors, Preservative Errors
	Dells-Kapian Executive Function System (D-KEFS)
	Subtests: Tower Test, Colour Interference, Trail Making Test, Letter Fluency, Verbai
	National Institutes of Health Teelbox (NIH Teelbox)
	Subtest: Dimensional Change Card Sort
	Test of Executive Control (TEC)
	Subtest: Non-Inhibitory Condition: Incorrect
	F-A-S Test
	Subtests: Letter Fluency and Category Fluency
	Other Measures: Trail Making Test Trial B
Working Memory	Wechsler Intelligence Scale for Children (WISC, Version III)
Included: At least one measure	Subtests: Digit Span, Forward Digit Span, Backward Digit Span, Freedom from
from each study reported.	Distractibility Index, Spatial Span Backwards, Working Memory Index, Digit AB
subdomains, and clinically	Cambridge Neuropsychological Test Automated Battery (CANTAB)
relevant outcomes prioritised	Subtests: Spatial Span Length, Spatial Span Backwards, Spatial Working Memory
when available.	Errors, Spatial Working Memory Strategy
	Test of Memory and Learning (TOMAL)
	Subtest: Digits Backwards
	Working Memory Test Battery (WMTB)
	Subtests: Digit Recall, Block Recall
	Junior South African Individual Scales (JSAIS)
	Subtests: Digit Span A (Forward), B Total Score (Backward), Digit Span AB Total
	Score
	Differential Ability Scales (DAS)
Adaptiva Dahaviaur	Sublest: Working Memory
Adaptive Behaviour Included: At least one measure from each study reported.	Subtosto: Composito, Socialization, Daily Living Skills, Communication
	Adaptive Rehaviour Assessment System (ARAS, Versions II and Caregiver)
	Subtests: Composite and Socialisation
	Scales of Independent Behaviour Revised (SIB-R, Versions Caregiver)
	Subtest: Composite
	Bayley Scales of Infant Development (BSID, Version III Caregiver)
Behaviour	Child Behaviour Checklist (CBCL, Versions Caregiver and Teacher)
Included: At least one measure from each study reported. Composite scores, relevant subdomains, and clinically relevant outcomes prioritised when available.	Subtests: Total Behaviour Scores, Internalising Behaviour, Externalising Behaviour.
	Teacher Report Form (TRF)
	Subtests: Total Behaviour Scores, Internalising Behaviour, Externalising Behaviour
	Adult Self-report (ASR)
	Subtests: Total Behaviour Scores, Internalising Behaviour, Externalising Behaviour
	Problem Behaviour Checklist – 36 (PBCL-36, Versions Caregiver and Teacher)
	Subtests: Total Behaviour Scores

	Strengths and Difficulties Questionnaire (SDQ, Versions Caregiver, Teacher, and
	Self-Report)
	Subtests: Total Behaviour Scores, Internalising Behaviour, Externalising Behaviour.
	Social Skills Rating Scale (SSRS, Versions Caregiver and Teacher)
	Subtests: Total Behaviour Scores, Internalising Behaviour, Externalising Behaviour.
	Behaviour Assessment System for Children (BASC, Versions II, III, and Caregiver)
	Subtests: Externalising Behaviour and Internalising Behaviour.
	Infant Behaviour Questionnaire (IBQ, Version Caregiver)
	Subtests: Externalising Behaviour (Surgency), Effortful Control, Negative Effect
	Vanderbilt (Caregiver Version)
	Subtest: Oppositional Defiant
	Disruptive Behaviour Disorder Rating Scales (DBD, Versions Caregiver and Teacher)
	Connors Behaviour Rating Scale (CBRS-P, Caregiver Version)
	Brief Infant-Toddler Social and Emotional Assessment (BITSEA, Caregiver Version)
	Subtests: Possible Problem and Possible Competence Deficit
Social	Child Behaviour Checklist (CBCL), Teacher Report Form (TRF) & Youth Self-report
Included: At least one measure	(YSR)
from each study reported.	Subtest: Social
subdomains, and clinically	Bayley Scales of Infant Development (BSID, Version III)
relevant outcomes prioritised	Subtest: Socio-Emotional
when available.	Social Problem-Solving Inventory–Revised (SPSI-R, Self-Report Version)
	Strengths and Difficulties Questionnaire (SDQ, Versions Caregiver, Teacher, Self-
	Report)
	Subtests: Peer Problems and Abnormal Prosocial Behaviour
	Behaviour Assessment System for Children (BASC, Caregiver Version)
	Subtest: Social
	Sociomoral Reflection Measure, Short Form (SRM-SF)
	Griffith Mental Development Scales (GMDS)
	Subtest: Personal-Social
	Social Skills Rating Scale (SSRS, Versions Caregiver and Teacher)
	Social Responsiveness Scale (SRS, Versions Caregiver)
	Vineland Social Maturity Scale (VSMS)
	Subtest: Social
	Children's Interpersonal Problem Solving (chIPS)
	A Developmental NEuroPSYchological Assessment (NEPSY, Versions I and II)
	Subtests: Theory of Mind Total, Verbal, and Contextual
	Reading the Mind's Eye (RtME)
Sensory Processing and	Infant-Toddler Sensory Profile
Soft Neurological Signs	Subtests: Low Registration, Sensation Seeking, Sensory Sensitivity, Sensation
Included: At least one composite	Avoiding
score measure from each study	Short Sensory Profile (SSP, Caregiver Version)
also reported. Subdomains were	Sensory Processing Measure (SPM, Home Scale Version)
studies.	Quick Neurological Screening Test (QNST, Version II)

# Table 5. Summary of structural and neurological neurodevelopmental outcomes

Outcome domain	Measures
Birth head circumference	Head circumference ≤10 <sup>th</sup> percentile
(also referred to as	Head circumference centiles
occipitofrontal	Head circumference (cm)
circumference, OFC)	
Postnatal head	Head circumference $\leq 10^{th}$ or $\leq 3^{rd}$ percentile
circumference (or OFC)	Head circumference centiles
	Head circumference (cm) ≤12 months of age (exposure studies)

	Head circumference (cm) >12 months of age (exposure studies)
	Head circumference (cm) 6-9 years of age (diagnosed studies)
	Head circumference (cm) 9-18 years of age (diagnosed studies)
Clinical MRI	Clinically significant incidental findings
Quantitative MRI	Total intracronial valume (total brain valume (cm <sup>3</sup> )
	Grey matter volume (cm <sup>3</sup> )
	White matter volume (cm <sup>3</sup> )
	Cortical grey matter volume (cm <sup>3</sup> )
	Subcortical grey matter volume (cm <sup>3</sup> )
	Cerebellar grey matter volume (cm <sup>3</sup> )
	Cerebellar white matter volume (cm <sup>3</sup> )
	Corpus callosum (Fractional anisotropy, FA)
	Hippocampus volume (mm <sup>3</sup> )
	Putamen volume (mm/cm <sup>3</sup> )
	Amygdala volume (mm/cm <sup>3</sup> )
	Caudate volume (mm <sup>3</sup> )
	Thalamus volume (cm <sup>3</sup> )
Seizures	Risk of neonatal seizures
	Risk of epilepsy
Cerebral palsy (CP)	Pre-perinatal acquired CP
	All CP types
Visual impairment	Severely impaired visual acuity (0.1-0.5)
	Abnormal visual abilities (not defined)
Hearing impairment	Abnormal hearing abilities (not defined)
	Multiple definitions of hearing impairment – children receiving medical treatment
	for hearing impairment, congenital or definitive cases of hearing impairment.

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## 3.2.2 Exclusion criteria

Articles were excluded if they were: preclinical studies, letters, editorials, conference abstracts, higher degree dissertations, reviews, or commentaries. Other exclusion criteria included: sample size <10; presentation of results split by sex; PAE measured using only biological markers; or lack of a comparison group of individuals with no/minimal PAE (for exposure studies) or typically developing control group (for diagnosed studies).

When multiple published studies were identified that reported on the same population or cohort and outcome over a similar timeframe, the study with the largest sample size for the respective outcome of interest was selected to avoid duplication of data. An exception was made if the study with the smaller sample size reported participant groupings with greater specificity (e.g., multiple PAE levels or FASD diagnostic subgroups).

A list of studies excluded after full-text screening, with reasoning, is provided in **Supplemental File A**.

## **3.3** Search strategy

Six electronic bibliographic databases were searched from inception until February 2021, and updated in February 2023: CINAHL, the Cochrane Library, EMBASE, PsychINFO, PubMed and Web of Science Core Collection. The search strategies applied to each database are provided in **Appendix A**.

Search terms included alcohol-related terms (and specifically those focussed on alcohol exposure during pregnancy) combined with terms related to the diagnostic criteria for FASD.

Retrieved references were imported into an EndNote library and duplicate records removed. Remaining references were uploaded to Covidence (<u>www.covidence.org</u>) for screening against the inclusion and exclusion criteria. Title and

abstracts were independently screened for eligibility by two reviewers. Full-text publications of the remaining references were then retrieved and independently assessed by two reviewers. Discrepancies were resolved via discussion and consensus with a third reviewer. Manual screening of reference lists of retrieved full-text publications and previous relevant systematic reviews were performed to identify relevant publications not identified by the initial search strategy.

## 3.4 Data extraction

Data extraction was performed independently by one reviewer and checked by a second reviewer using a standardised protocol. Disagreement was resolved by discussion with a third reviewer. Data recorded from the eligible studies included: first author's surname, publication year, study country, cohort (where relevant), study design, setting, sample characteristics, PAE groupings (for exposure studies), FASD diagnosis and diagnostic criteria (for diagnosed studies), comparison group, statistical associations, and covariate adjustments and/or sample matching to address confounders.

## 3.4.1 Grouping of exposure studies

PAE was classified into six categories:

- 1) light PAE (up to 20 g alcohol per week, equivalent to 2 standard drinks in Australia)
- 2) moderate PAE (21-100 g alcohol per week)
- 3) heavy PAE (101-200 g alcohol per week)
- 4) very heavy PAE (>200 g alcohol per week)
- 5) any PAE (exposure dichotomised as 'yes' or 'no')

6) confirmed/unquantifiable PAE (PAE was confirmed, however data on level of PAE were not reliably collected). Often these studies were reported to be heavy or very heavy levels of PAE, but not enough information was provided to allow accurate quantification into these exposure groups. However, this exposure level was important to include as it represents a common clinical presentation where specific levels of PAE can be unavailable.

These exposure levels were based on the Australian Guidelines to Reduce Health Risks from Drinking Alcohol (National Health and Medical Research Council (NHMRC), 2020) as well as a composite method developed to capture different patterns of alcohol use during pregnancy (O'Leary et al., 2010). Where available, mean prenatal alcohol consumption reported in each study was used to classify PAE according to these definitions. In instances where group means were not reported, available PAE data was used to calculate group means as per Patra et al. (2011). See **Appendix B** for an example of how PAE level was quantified. Therefore, author-defined exposure categories across included studies were not necessarily used. Instead, all studies with PAE were assessed and data grouped according to our pre-defined exposure category definitions. This enabled a standardised approach across all exposure studies. Where multiple author-defined exposure categories were classified into one of our pre-defined groupings, the group with the higher level of PAE was used.

## 3.4.2 Grouping of diagnosed studies

For diagnosed studies, FASD was classified into four diagnostic categories:

- 1) FASD (i.e., where studies grouped all individuals with any FASD diagnostic outcome together)
- 2) FAS (i.e., fetal alcohol syndrome (FAS), FASD with 3 sentinel facial features, syndromal, and FAS/partial FAS (pFAS) with FAS majority)
- 3) pFAS (i.e., pFAS and FAS/pFAS with pFAS majority)
- 4) ARND/Other (i.e., alcohol related neurodevelopmental disorder (ARND), static encephalopathy/alcohol exposed (SE/AE), neurobehavioural disorder/alcohol exposed (ND/AE), heavily exposed non-syndromal)

Definitions for the various FASD diagnostic terms were based on what was reported in each of the included studies. Wherever possible (i.e., where data were reported separately for each of these groups) all diagnostic groups were extracted. Where a study reported a combined FAS/pFAS group, it was classified as 'FAS' or 'pFAS' depending on which diagnosis was the majority within the group. If specific numbers were not reported, the study was classified in the 'pFAS' category. If a study reported multiple ARND/Other groups, SE/AE was used in favour of ND/AE and ARND was used in favour of heavily exposed.

## 3.5 Risk of bias assessment

Risk of bias assessment was performed independently by two reviewers and checked by a third reviewer using a modified version of the RTI Item Bank for Assessing Risk of Bias and Confounding for Observational Studies of Interventions or Exposures (Viswanathan et al., 2013). Ten items were included assessing selection bias, detection bias, performance bias, attrition bias and confounding. Risk of bias was assessed at the outcome level. Therefore, where relevant, studies that reported multiple outcomes were assessed for risk of bias multiple times for the different outcomes and analyses (e.g., raw data and regression analyses). Overall risk of bias was rated as low, moderate, serious, or critical.

- Studies were rated as *low* risk of bias if there were no concerns across all areas of the assessment.
- Studies were rated as *moderate* risk of bias if they had some minor methodological concerns, but no major methodological concerns.
- Studies were rated as *serious* risk of bias if they had one or more major methodological flaws or five or more areas where enough information was not provided.
- Studies were rated as *critical* risk of bias and excluded from analysis if they did not measure and even partially consider confounding variables.

## 3.6 Data analysis

Meta-analyses were conducted to investigate the effects of PAE exposure and FASD diagnosis on outcomes. Effect estimates were pooled across studies (when  $\geq 2$  studies) using a random effects model and study weightings were adjusted using the generic inverse-variance method (GIVM). Analyses were undertaken using the Review Manager 5.4 software (RevMan desktop, Cochrane, London, UK). Separate meta-analyses were conducted at each category of exposure (exposure studies) or for each diagnostic category where available. We acknowledge that associations between diagnostic outcomes and FASD diagnoses are often interdependent (i.e., an association will exist as the outcome was integral to the diagnostic process). However, we have included these studies due to variability in diagnostic criteria and to provide a complete analysis of all available evidence. Given this limitation, exposure studies will be prioritised when making recommendations and conclusions based on available evidence.

#### 3.6.1 Measures of association

For meta-analyses of binary outcomes, odds ratios or frequency data were used. Where available, adjusted odds ratios were preferred over crude/unadjusted odds ratios due to adjustment for confounding factors.

For meta-analyses of continuous data, means/standard deviations or mean differences were used. Where available, adjusted values were preferred over unadjusted.

For studies reporting regression analyses, a narrative synthesis was used.

## 3.6.2 Subgroup analyses

Subgroup analyses were used where there were enough studies available, to examine the effect of risk of bias (low versus moderate-high risk of bias) and adjustment for confounders (adjusted versus unadjusted statistical estimates). Subgroup analysis using timing of PAE was unable to be performed due to lack of available data regarding exposure timing or inconsistency in the timing data available.

## **3.7** GRADE assessment

Certainty of evidence for each meta-analytic finding was made using the GRADE approach (Guyatt et al., 2008). The following domains were assessed, and a judgement made as to whether there were 'serious' or 'not serious' concerns:

- **1. Risk of bias**: A 'serious' rating was provided when >50% of the studies included in a meta-analysis had a moderate or high risk of bias.
- Inconsistency: A 'serious' rating was provided when the overall heterogeneity chi-square statistic was significant (p<.05) and I<sup>2</sup> was >50%. Where the outcome included only a single study, inconsistency was rated as 'not serious'.
- **3.** Indirectness: A 'serious' rating was provided when >50% of studies included samples not likely to be comparative to an Australian population (e.g., all studies were undertaken in South Africa, Ukraine, or Chile).
- 4. Imprecision: A 'serious' rating was provided when the overall 95% CIs for the meta-analysis crossed the line of no effect, were wide or when optimal sample size criteria were not met (i.e., for dichotomous data, ≥300 abnormal events or sample size ≥2000; for continuous data, required sample size of ≥400). A 'very serious' rating was provided when all three 'serious' criteria above were present. 95% CIs were considered 'wide' based on clinically meaningful differences between the lower and upper confidence intervals for each of the outcomes (following discussion with clinical members of the Guidelines Development Group).
- 5. Other considerations: Publication bias was assessed with funnel plots generated for outcomes with 10 or more studies. Publication bias was rated as 'strongly suspected' in the presence of an asymmetrical funnel plot.

GRADE Profiler (GRADEPro, McMaster University and Evidence Prime, 2022) was used to complete the assessments and generate the overall GRADE rating for each meta-analytic outcome. The GRADE approach for prognostic factors was used whereby ratings started out as high certainty and were rated down due to the GRADE domains mentioned above. Overall GRADE ratings for each meta-analysis were reported in summary figures as:  $\oplus \bigcirc \bigcirc \bigcirc$  very low certainty,  $\oplus \oplus \bigcirc \bigcirc$  low certainty,  $\oplus \oplus \oplus \bigcirc$  moderate certainty, and  $\oplus \oplus \oplus \oplus$  high certainty.

## 3.8 Data presentation

Information from meta-analyses (i.e., number of studies (s), number of participants (n), pooled effect estimates, 95% confidence intervals (CI), and I<sup>2</sup> %), as well as the overall GRADE ratings for each meta-analysis, were presented in composite figures. This allowed data to be compared visually across PAE levels and FASD diagnoses. For physical size, where there was only a single study across all exposure levels or diagnoses for an outcome, these were generally not included in the summary figures. However, all single studies are reported in the associated Supplemental File for each domain. For functional neurodevelopment, due to diversity of measures and outcome type, only the most clinically relevant outcomes, even where there was only a single study, are included in the summary figures and results for other outcomes are provided in the associated Supplemental File. For dysmorphology and neurological outcomes, aside from head circumference measures, single studies have been included in the summary figures due to limited data available.

## 4. Results

## 4.1 Search results

The initial search identified 18,422 records. After the removal of 10,704 duplicates, 7,718 records underwent title and abstract screening. A further 7,095 records were excluded, leaving 623 articles eligible for screening at the full-text level. Of these records, 384 were excluded. Two additional studies were removed due to critical risk of bias. See **Supplemental File A** for the full list of articles excluded at the full-text level with reasoning. Reference list searches led to the inclusion of an additional 49 articles and an updated search before submission yielded 20 articles. In total, 306

studies were included in this systematic review. Physical size outcomes included 106 studies, dysmorphology measures were reported in 43 studies, functional neurodevelopmental outcomes were included in 195 studies, and structural and neurological measures reported in 110 studies. There were 20 studies that only reported regression analyses. An overview of the search results is presented in **Figure 1**.

## 4.2 Study characteristics

Study characteristics are presented in **Appendix C**. Studies originated from 23 countries, including 136 (44%) from USA, 44 (14%) from Europe/UK, 42 (14%) from South Africa, 41 (13%) from Canada, 20 (7%) from Australia/New Zealand, 5 (2%) from Japan and 7 (2%) from other countries. Eleven studies (4%) were multinational. Of the 306 included studies, 216 (71%) were case-controls (99 nested case-controls) and 90 (29%) were cohort studies (82 prospective and 8 retrospective). One-hundred and forty-five (33%) of the case-controls and 90 (100%) of the cohorts were exposure studies. **Figure 1** provides an overview of the outcome domains included.

## 4.3 Risk of bias

A total of 505 risk of bias assessments were completed. Overall, 71.3% (n = 360) of outcomes were rated as serious, 21.2% (n = 107) rated as moderate, and 6.5% (n = 33) were rated as low risk of bias. Two studies (Blanck-Lubarsch et al., 2020; Kvigne et al., 2004) were rated as critical risk of bias and were excluded from further analysis. At the outcome domain level, for physical size 64.4% (n = 76) were rated as serious, 27.1% (n = 32) rated as moderate and 7.6% (n = 9) were rated as low risk of bias. For dysmorphology, 85.4% (n = 41) were rated as serious, 12.5% (n = 6) rated as moderate and no studies were rated as low risk of bias. For functional neurodevelopmental outcomes, 71.2% (n = 153) were rated as serious, 19.5% (n = 42) rated as moderate and 8.8% (n = 19) rated as low risk of bias. For structural and neurological outcomes, 72.6% (n = 90) were rated as serious, 21.8% (n = 27) rated as moderate and 4% (n = 5) rated as low risk of bias. See **Supplemental File B** for an overview of all ratings. In particular, studies were rated as having serious risk of bias if they did not adequately control for confounding variables, did not have reliable assessments of PAE or did not report enough details to assess risk of bias across multiple areas.



Figure 1: Flow chart showing search results, screening and selection of studies for inclusion in the systematic review of FASD diagnostic components. For database searches; ti = title, ab = abstract, and kw = keyword. # refers to studies where exclusion reasons differed based on the outcome being examined (see Supplemental File A for further details). Risk of bias was assessed using a modified version of the RTI Item Bank for Assessing Risk of Bias and Confounding for Observational Studies of Interventions or Exposures (Viswanathan et al., 2013). \*refers to the presence of studies included in both the exposure and diagnosed groups (n = 3). Note that some studies reported on more than one diagnostic domain.

### 4.4 Review findings and GRADE quality assessments

#### 4.4.1 Physical size

Figures 2 to 5 provide an overview of the physical size meta-analysis results. See Supplemental File C for detailed GRADE summary tables and individual forest plots and Supplemental File D for a narrative summary of regression data. Overall, for the physical size domain, there were 104 meta-analyses with 1 to 14 studies (Mean = 3.9; Mode =1) included per meta-analysis. For those outcomes with 5 or more studies included in the meta-analysis (n = 31), 48.4% had high heterogeneity across studies (i.e.,  $l^2 > 75\%$ ). For outcomes with  $\geq 10$  studies included in the meta-analysis (n = 10), the available funnel plots showed no evidence of publication bias (Supplemental File C).

Overall, there was a dose-response association between the level of PAE or severity of FASD diagnosis and physical size outcomes. At birth, pooled effect estimates indicated that PAE at heavy and very heavy levels were associated with increasingly higher odds of small for gestational age (moderate certainty) and low birth weight (low to moderate certainty), and PAE at heavy, very heavy and confirmed unquantifiable levels were inversely related to mean birth weight and birth length (very low to low certainty; **Figure 2**). FASD, FAS and pFAS diagnoses were also associated with lower mean birth weight and birth length (very low to moderate certainty; **Figure 3**).

Postnatally, very heavy and confirmed unquantifiable PAE were associated with increased odds of weight and height <10<sup>th</sup> percentile (low certainty; **Figure 4**). PAE associations with mean weight and height outcomes produced more variable results and had less studies and participants available to examine. Diagnoses of FAS, pFAS and ARND/Other were associated with lower weight and height when children were aged 6-9 years, as well as later in adolescence (9-18 years of age; very low to low certainty; **Figure 5**).

## 4.4.2 Dysmorphology

**Figures 6 to 9** provide an overview of the dysmorphology meta-analysis results. See **Supplemental File E** for detailed GRADE summary tables and individual forest plots, and **Supplemental File D** for a narrative summary of regression data. Overall, for the dysmorphology domain there were 58 meta-analyses with 1 to 12 studies (Mean = 2.1; Mode = 1) included per meta-analysis. For those outcomes with 5 or more studies included in the meta-analysis (n = 16), 1.9% had high heterogeneity (i.e.,  $l^2 > 75\%$ ). For outcomes with  $\geq 10$  studies included in the meta-analysis (n = 3), the available funnel plots showed no evidence of publication bias (**Supplemental File E**).

The three sentinel facial features of FASD were examined relative to exposure level (**Figure 6A**) and FASD diagnosis (**Figure 6B**). Although there was low to very low certainty in the evidence, meta-analysis generally indicated an increased odds of presentation of a smooth philtrum, thin vermilion, and short palpebral fissures with PAE exposure. There were mostly only single studies available, except for where the exposure was confirmed but unquantifiable. The one study with heavy PAE had high variability (wide 95% CI; **Figure 6A**). There were no studies that included light PAE levels. Diagnostic groups that included the sentinel facial features as part of their criteria showed significant associations, with higher variability for the general FASD group, particularly when a less stringent cut-off was used for short palpebral fissure length (i.e., <10<sup>th</sup> percentile; **Figure 6B**).

There were very few PAE studies examining minor facial (**Figure 7A**) and non-facial dysmorphic features (**Figure 7B**). Although reported across three studies (Autti-Rämö et al., 1992; Bandoli et al., 2020; Golden et al., 1982), only single studies were available for each outcome/PAE level. There was very low to low certainty in the evidence for an association of PAE with these minor dysmorphic features, often with substantial variability across outcomes. Associations between FASD and minor facial (**Figures 8A**) and non-facial dysmorphic features (**Figures 8B**) were also examined. Generally, individuals with FAS were found to have higher odds of experiencing minor dysmorphic features compared to pFAS and ARND/Other groups. While there were more diagnosed studies available compared to exposure studies, 6 out of 58 outcome/diagnosis associations had only 1 study available.

A small number of studies were identified that reported composite dysmorphology scores (**Figure 9**). Two studies were available that examined moderate and/or very heavy PAE (Bandoli et al., 2020; Coles et al., 1991), with both showing significant associations between PAE and dysmorphology scores (**Figure 9A**). As expected, studies including dysmorphology in the diagnosis showed a positive association with dysmorphology score (**Figure 9B**).



**Figure 2:** Association between prenatal alcohol exposure (PAE) and various measures of size at birth. A) Small for gestational age; B) low birth weight; C) birth weight; and D) birth length. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc \bigcirc =$  low certainty;  $\bigcirc \bigcirc \bigcirc \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. OR = Odds Ratio [95% Confidence Interval]; l<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



**Figure 3.** Association between fetal alcohol spectrum disorder (FASD) diagnoses and birth measures. A) Birth weight; and B) birth length. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \oplus \oplus \bigcirc \bigcirc =$  moderate certainty; s = number of studies included in each meta-analysis; n = overall number of participants included in each meta-analysis; MD = Mean difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4); FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



Figure 4. Association between prenatal alcohol exposure (PAE) and various measures of postnatal size. A) Weight <10<sup>th</sup> percentile; B) height <10<sup>th</sup> percentile; C) weight at <12 months of age or >12 months of age or >12 months of age. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty;  $\bigcirc \bigcirc \bigcirc =$  moderate certainty; s = number of studies included in each meta-analysis; n = overall number of participants included in each meta-analysis; OR = Odds Ratio [95% Confidence Interval (CI)]; MD = Mean difference [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



**Figure 5.** Association between fetal alcohol spectrum disorder (FASD) diagnoses and various measures of postnatal size. A) Weight <10<sup>th</sup> percentile; B) height <10<sup>th</sup> percentile; C) weight at 6-9 years or 9-18 years of age; D) height at 6-9 years or 9-18 years of age; E) weight (percentiles); and F) height (percentiles). *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \oplus \bigcirc \bigcirc =$  noderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. OR = Odds Ratio [95% Confidence Interval (CI)]; MD = Mean difference [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 6:** Association between prenatal alcohol exposure (PAE), fetal alcohol spectrum disorder (FASD) diagnosis and sentinel facial features. A) Exposure studies examining smooth philtrum (3 or 4+ on Lip-Philtrum Guide), thin vermilion (3 or 4+ on Lip-Philtrum Guide), and short palpebral fissures (<10<sup>th</sup> percentile for very heavy, moderate, and confirmed unquantifiable PAE and <3<sup>rd</sup> percentile for heavy PAE); and B) diagnosed studies examining smooth philtrum (4+ on Lip-Philtrum Guide), thin vermilion (4+ on Lip Philtrum Guide), and short palpebral fissures (<3<sup>rd</sup> or 10<sup>th</sup> percentile). *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty. s = number of studies included in meta-analysis. n = overall number of participants included in the meta-analysis. OR = Odds Ratio [95% Confidence Interval]. I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 7:** Association between prenatal alcohol exposure (PAE) and minor dysmorphology features. A) Minor facial dysmorphology; and B) non-facial dysmorphology. Features are described in detail in Hoyme et al. (2016). *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc \bigcirc$  = low certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. OR = Odds Ratio [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



**Figure 8:** Association between fetal alcohol spectrum disorder (FASD) diagnoses and minor dysmorphology features. A) Minor facial dysmorphology; and B) non-facial dysmorphology. Features are described in detail in Hoyme et al. (2016). *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty e;  $\bigcirc \bigcirc \bigcirc =$  low certainty. S = number of studies included in each meta-analysis. N = overall number of participants included in each meta-analysis. OR = Odds Ratio [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 9:** Association between prenatal alcohol exposure (PAE), fetal alcohol spectrum disorder (FASD) diagnosis and dysmorphology scores. A) Exposures studies; and B) diagnosed studies. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc \bigcirc =$  low certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.

#### 4.4.3 Functional neurodevelopmental outcomes

**Figures 10 to 25** provide an overview of the functional neurodevelopmental meta-analysis results. See **Supplemental File F** for detailed GRADE summary tables and individual forest plots, and **Supplemental File D** for a narrative summary of regression data for these outcomes in included studies. There were 663 meta-analyses with 1 to 16 studies (Mean = 1.8; Mode = 1) included per meta-analysis. For those outcomes with 5 or more studies included in the meta-analysis (n = 37), 45.9% had high heterogeneity across studies (i.e.,  $l^2 > 75\%$ ). For outcomes with  $\geq 10$  studies included in the meta-analysis (n = 3), the available funnel plots showed no evidence of publication bias (**Supplemental File F**). For exposure studies, very few reported on light or moderate PAE levels. As mentioned in Section 3.6, the association of many of these behavioural outcomes with diagnostic groups is to be expected given inclusion in the diagnostic process.

#### Attention

Caregiver-reported attention problems were significantly associated with very heavy and confirmed unquantifiable PAE when reported as a standardised mean difference, but this evidence had a very low to low certainty ratings (**Figure 10A**). However, when this outcome was reported as an OR, results were more variable and there was no significant association with PAE at light to heavy levels (**Figure 10B**). All diagnostic groups demonstrated increased attention problems on both caregiver and teacher report, although there was wide variability found for the pFAS group on caregiver reports and very low to moderate certainty (**Figure 10C**). Significantly lower NEPSY Auditory Attention and Response Set were found for FASD groups compared to controls and no significant differences found for the two studies assessing sustained attention, although all had ratings of very low certainty (**Figure 10D**).

#### Behaviour

Very heavy and confirmed unquantifiable PAE were associated with increased total behavioural problems and externalising behaviour problems on the CBCL, while results were more variable for internalising behaviour problems, all with low to very low certainty ratings (Figure 11A). Confirmed unquantifiable PAE was also associated with increased behaviour problems on all subscales of the CBCL (Figure 11B). Odds of scoring in the clinical range for behavioural problems on the CBCL or SDQ (definitions varied between studies) were increased only at moderate PAE levels, with evidence from single studies reporting on heavy and light PAE demonstrating variable effects. This evidence had moderate certainty (Figure 11C).

In diagnostic groups, all demonstrated increased rates of total behaviour problems as reported by caregivers and teachers, although associations were more variable when separated into externalising and internalising behaviour scores based on caregiver reports (**Figure 12A-B**). However, FASD diagnosis was consistently associated with increased behaviour problems measured across most instruments and subdomains, irrespective of whether this was based on teacher or caregiver report (**Figures 12 and 13**). The evidence for an association between a FASD diagnosis of some description and a clinically relevant behavioural problem was generally of moderate certainty.

#### Executive function and working memory

For heavy and confirmed unquantifiable PAE, there was an association with worse scores on most direct executive functioning and working memory measures, with a very low to moderate certainty in this evidence (**Figures 14 & 15**). However, no association for light, moderate or heavy levels of PAE on parent or teacher reported everyday EF abilities (**Figure 16A**).

Most diagnosed groups demonstrated poorer performance compared to controls on measures of executive function and working memory, with very low to low certainty in this evidence (**Figures 14B, 15C-D & 16B**). This was irrespective of whether the assessment instrument was based on a direct measure or caregiver or teacher report and highlights that all diagnostic groups can have significant challenges with executive functioning.



**Figure 10:** Association between prenatal alcohol exposure (PAE), fetal alcohol spectrum disorder (FASD) diagnosis and measures of attention. A) Exposure studies using child behaviour checklist (CBCL); B) exposure studies using CBCL (odds ratio; cut-offs not reported); C) diagnosed studies using CBCL and teacher report form; and D) diagnosed studies using A Developmental NEuroPSYchological Assessment (NEPSY), Selective/Sustained Measures (Test of Everyday Attention for Children-5 and the Neurobehavioral Evaluation System) and Disruptive Behaviour Disorder Rating Scales (DBD). Lower scores indicate better performance for all measures except for NEPSY measures. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc \bigcirc$  = low certainty;  $\oplus \oplus \oplus \bigcirc \bigcirc$  = moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; l<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 11:** Association between prenatal alcohol exposure (PAE) and caregiver reported measures of behaviour. A) Child behaviour checklist (CBCL) composite scores; B) CBCL sub-scale scores; and C) CBCL and Strengths & Difficulties Questionnaire (SDQ; odds of scoring in 'clinical range'/'abnormal scores'/CBCL scores >60). Lower scores indicate better performance in all reported measures. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc \bigcirc =$  very low certainty;  $\oplus \oplus \bigcirc \bigcirc =$  low certainty;  $\oplus \oplus \oplus \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



**Figure 12:** Association between fetal alcohol spectrum disorder (FASD) diagnosis and composite measures of behaviour. A) Caregiver child behaviour checklist (CBCL) and problem behaviour checklist-36 (PBCL-36); and B) reports teacher report form (TRF), PBCL teacher report form, and social skills rating system (SSRS). Lower scores indicate better performance in all reported measures. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty;  $\bigcirc \bigcirc \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 13:** Association between fetal alcohol spectrum disorder (FASD) diagnosis and sub-domain measures of behaviour. A) Child behaviour checklist (CBCL), Connors Behaviour Rating Scale (CBRS-P), social skills rating system (SSRS) and Disruptive Behaviour Disorder Rating Scales (DBD); and B) reports CBCL, Teacher Report Form (TRF), SSRS and DBD. Lower scores indicate better performance in all reported measures. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty;  $\bigcirc \bigcirc \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



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**Figure 14:** Association between prenatal alcohol exposure (PAE), fetal alcohol spectrum disorder (FASD) diagnosis and measures of working memory. A) exposure studies using the Wechsler Intelligence Scale for Children (WISC-III) and Cambridge Neuropsychological Test Automated Battery (CANTAB); B) reports diagnosed studies using the WISC-III/IV, CANTAB, Junior South African Individual Scales (JSAIS), Working Memory Test Battery (WMTB), Test of Memory and Learning (TOMAL). Higher scores indicate better performance except for Spatial Working Memory Strategy. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty;  $\bigcirc \bigcirc \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 15:** Association between prenatal alcohol exposure (PAE), fetal alcohol spectrum disorder (FASD) diagnosis and measures of executive functioning. A) Exposure studies using NEuroPSYchological Assessment (NEPSY) Speeded Naming and Wisconsin Card Sorting Test (WCST); B) exposure studies using Delis-Kaplan Executive Function System (D-KEFS); C) diagnosed studies using NEPSY inhibition naming (INN), inhibition inhibition (INI) and inhibition switching (INS); D) Diagnosed studies using Delis-Kaplan Executive Function System (D-KEFS) and another Trail Making Test Trial B. Higher scores indicate better performance except for Trail Making Test Trial B. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc =$  every low certainty;  $\oplus \oplus \bigcirc =$  noderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.


Figure 16: Association between prenatal alcohol exposure (PAE), fetal alcohol spectrum disorder (FASD) diagnosis and parent and teacher measures of every day executive function abilities. A) Exposure studies examining caregiver and teacher Behaviour Rating Inventory of Executive Function (BRIEF); B) diagnosed studies examining caregiver and teacher Behaviour Rating Inventory of Executive Function (BRIEF); B) diagnosed studies examining caregiver and teacher Behaviour Rating Inventory of Executive Function (BRIEF); B) diagnosed studies examining caregiver and teacher Behaviour Rating Inventory of Executive Function (BRIEF). Lower scores indicate better performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc \bigcirc$  = low certainty;  $\oplus \oplus \oplus \bigcirc \bigcirc$  = moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder; GEC = General Executive Composite.

# Language

For exposure studies, there were generally only single studies available for each outcome/ instrument and no significant associations across light and moderate levels (**Figure 17A, C**). However, confirmed unquantifiable PAE did show associations with poorer language abilities compared to non-exposed controls, with very low to low certainty (**Figures 17B**). Diagnosed groups demonstrated poorer language performance compared to controls, except for studies using the NEPSY, where scores were variable (**Figure 18A**). Certainty for diagnosed studies was very low to low.

#### Motor

Exposure studies reported on potential associations with measures of motor function across all exposure levels (**Figure 17D, E**). However, only very heavy PAE was associated with significant reductions in motor abilities, although this was only measured in infants and pre-school age children (**Figure 17D**). Diagnosed groups generally demonstrated poorer motor abilities compared to controls, although studies reporting data as ORs showed highly variable/imprecise results (i.e., very wide 95% Cls; **Figure 18B-D**). All evidence for this domain was rated as being of very low to low certainty.

#### Academic

The association between PAE and academic achievement was examined across all exposure levels and an inverse dose response between academic ability and exposure level was found (**Figure 19A**). However, there were generally only single studies available for each outcome/level analysis (**Figure 19A**). Certainty of the evidence ranged from very low to moderate. There were more studies available to examine the association with FASD diagnosis, and consistent with the exposure studies, there was generally an inverse relationship between the severity of the diagnosis and academic ability (**Figure 19B**). This was particularly evident when broken down into reading/literacy and numeracy/maths outcomes (**Figure 19B**). The certainty of the evidence was as per the exposure studies.

#### Memory

For this outcome, there were generally only single exposure studies across various levels of PAE, including light and moderate, with heavy and confirmed unquantifiable PAE associated with significantly poorer memory abilities (**Figure 20A**). Certainty of evidence ranged from very low to moderate. FASD diagnosis was associated with significantly poorer memory scores across both verbal and non-verbal memory measures, with very low to low certainty (**Figure 20B-C**).

# Intellectual abilities

Exposure studies ranged across all exposure levels but only confirmed unquantified PAE and very heavy PAE was significantly associated with lower IQ scores (**Figure 21**). This was across various subs-scales including performance and non-verbal IQ. However, there was only low to very low certainty for this evidence. All FASD diagnoses were associated with lower full-scale, verbal, non-verbal and performance sub-scale IQ scores (**Figure 21**). Studies reporting these measures as percentiles were rated as higher certainty evidence (low to moderate) compared to those reporting standard scores (very low to low).

# Adaptive behaviour and social functioning

Very few exposure studies reported outcomes in this sub-domain, with typically only single studies at various levels of exposure, including light and moderate. However, there were more studies with confirmed unquantified PAE, and this level of exposure was associated with lower scores on all measures of adaptive behaviour and higher scores for social problems, with very low certainty of this evidence (**Figure 23A, B**). At other PAE levels, no significant associations were found, with low to moderate certainty of this evidence (**Figure 23B, C**). FASD diagnosis was associated with significantly lower adaptive functioning abilities and increased social problems, although more variable results were found for the caregiver reports compared to the teacher reports (**Figure 24**). Only diagnosed studies were available assessing theory of mind, with variable results found (**Figure 24A**).

# Sensory processing and soft neurological signs

There were only single exposure outcomes (all moderate PAE level and only infants and young children from two studies), with no evidence of significant associations and low to moderate certainty of this evidence (Figure 25A). Similarly, there were only single outcomes available from two studies examining associations between FASD diagnosis and outcomes. There were increased challenges with sensory processing in children diagnosed with FASD, although there was often low precision of the estimates, particularly when expressed as an OR (Figure 25B-C). There were also generally more concerns on the Quick Neurological Screening Test, with low certainty of this evidence (Figure 25B-C).



**Figure 17:** Association between prenatal alcohol exposure (PAE) and language and motor measures. A) Bayley's Scales of Infant Development (BSID-III) language; B) Clinical Fundamentals of Language Preschool (CELF-P), Peabody Picture Vocabulary Test-Revised (PPVT-R) and NEuroPSYchological Assessment (NEPSY) word generation and phonological processing; C) Ages and Stages Language and CELF-5; D) BSID-III motor and Beery Buktenica Developmental Test of Visual Motor Integration (VMI) and E) Movement Assessment Battery for Children (M-ABC). Higher scores indicate better test performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc =$  very low certainty;  $\oplus \oplus \bigcirc \bigcirc =$  low certainty;  $\oplus \oplus \oplus \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



**Figure 18:** Association between fetal alcohol spectrum disorder (FASD) diagnosis and language and motor measures. A) Clinical Fundamentals of Language Preschool (CELF-4), Peabody Picture Vocabulary Test-Revised (PPVT-R), NEuroPSYchological Assessment (NEPSY) word generation (letters) and comprehension of instructions, Rustioni Test of Language Comprehension, Test of Language Competence, and Test of Language Development; B) Griffith Mental Development Scales (GMDS), Bruininks-Oseretsky Test of Motor Proficiency (BOTMP/BOT-2), Clinical Observations of Motor and Postural Skills (COMPS) and Beery Buktenica Developmental Test of Visual Motor Integration (VMI); C) grooved pegboard test (GPT) completion time; and D) reports Movement Assessment Battery for Children (M-ABC) (odds <5<sup>th</sup> percentile), BOT-2 (odds <1SD, <2SD and <3<sup>rd</sup> percentile). A, B) lower scores indicate better performance except for Rustioni Errors. C, D) higher scores indicate better performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc$  = low certainty;  $\oplus \oplus \bigcirc$  = moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; l<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 19:** Association between prenatal alcohol exposure (PAE) or fetal alcohol spectrum disorder (FASD) diagnosis and academic achievement. A) Exposure studies and B) diagnosed studies reporting measures of overall academic achievement and sub-tests for literacy/reading and numeracy/maths abilities. Specific tests used in A: Wide Range Achievement Test-Revised (WRAT-R) reading and arithmetic sub-scales, Wechsler Individual Achievement Test (WIAT-II) word reading and maths sub-scales, Kaufman Assessment Battery for Children (K-ABC) reading and maths sub-scales and the Wechsler Intelligence Scale for Children (WISC-IV) arithmetic sub-scale. Specific tests used in B: Bracken Basic Concept Scale, K-ABC academic composite, WIAT-II numerical operations sub-scale, WRAT-3 and 4 reading and arithmetic subscales, Woodcock Johnson quantitative concepts and reading mastery, Observation Questionnaire for the Early Identification of Learning Difficulties, and Key State 2 UK National Curriculum Assessment. Higher scores indicate better performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc \bigcirc$  = moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 20:** Association between prenatal alcohol exposure (PAE) or fetal alcohol spectrum disorder (FASD) diagnosis and measures of memory. A) Exposure studies examining verbal memory; B) diagnosed studies examining verbal memory and visual/verbal memory; C) diagnosed studies examining non-verbal memory. Specific assessments used in A: Rey Auditory Verbal Learning Test (RAVLT), A NEuroPSYchological Assessment (NEPSY), California Verbal Learning Test - Children's Version (CVLT-C), Kaufman Assessment Battery for Children (K-ABC), Rey Complex Figure Test and Recognition Trial (RCFT); specific assessments used in B: Wide Range Assessment of Memory and Learning (WRAML) story memory, Story Memory, Children's Memory Scale (CMS)-Stories, CVLT-C, Verbal Selective Reminding Task (VSRT), K-ABC, NEPSY-II Memory for Names, Memory of 16 objects); specific assessments used in C: Rey Complex Figure Test and Recognition Trial (RCFT), CANTAB Pattern Recognition, Nonverbal Selective Reminding Memory Test (NVRST), Test of Memory and Learning (TOMAL). Higher scores indicate better performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc \bigcirc$  = low certainty;  $\oplus \oplus \oplus \bigcirc$  = moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). ARND = alcohol related neurodevelopmental disorder.



**Figure 21:** Association between prenatal alcohol exposure (PAE) and general intellectual abilities. A) Full-scale IQ, performance IQ and verbal IQ; B) Non-verbal IQ, and C) Composite IQ. Children aged 4-17 years in A) and B); and infants in C). Specific tests used in A) include Wechsler Intelligence Scale for Children (WISC III, IV & R) full, verbal and performance scales, Wechsler Preschool and Primary Scale of Intelligence (WPSI-R) full, verbal and performance scales, Wechsler Adult Intelligence Scale (WAIS-II) full, verbal and performance scales, McCarthy Scales of Children's Abilities (MSCA) general cognitive index, Kaufman Brief Intelligence Test (K-BIT) composite and verbal sub-scale, Kaufman Assessment Battery for Children (K-ABC) mental composite, and Differential Ability Scales (DAS-II) general cognitive index. Specific tests used in B) include Leiter International Performance Scale, Raven's Coloured Progressive Matrices, DAS-II non-verbal composite, K-ABC non-verbal sub-scale, K-BIT non-verbal sub-scale. Specific tests used in C) include Bayley's Scale of Infant Development (BSID-II and III) mental/cognitive index. Higher scores indicate better performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc$  = very low certainty;  $\oplus \oplus \bigcirc \bigcirc$  = low certainty;  $\oplus \oplus \bigcirc$  = moderate certainty. s = number of studies included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



**Figure 22:** Association between fetal alcohol spectrum disorder (FASD) diagnoses and general intellectual abilities. A) Full-scale IQ, verbal IQ, non-verbal IQ and performance IQ, and B) general ability, verbal ability and non-verbal ability. Individuals aged 5-32 years in A) and children aged 6-7 years in B). Specific tests in A) include Wechsler Intelligence Scale for Children (WISC-IV) full, verbal and performance scales, Wechsler Adult Intelligence Scale (WAIS-R) full, verbal and performance scales, Malin's Intelligence Scale for Indian Children (MISIC) full, verbal and performance scales, Kaufman Brief Intelligence Scale (K-BIT), Leiter International Performance Scale-Revised, Raven's Coloured Progressive Matrices, Test of Non-Verbal Intelligence (TONI) and Test for Reception of Grammar (TROG) verbal IQ scale. Specific tests in B) include Differential Ability Scales (DAS-II). Higher scores indicate better performance. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc =$  very low certainty;  $\oplus \oplus \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS is partial fetal alcohol syndrome; ARND = alcohol related neurodevelopmental disorder.



**Figure 23:** Association between prenatal alcohol exposure (PAE) and adaptive and social behaviour. A) Caregiver-reported adaptive behaviour; B) caregiver-reported and self-reported social problems; C) caregiver-reported social problems (odds of 'clinical range scores'/ 'borderline or abnormal scores'/cut-offs unclear). Specific assessments used in A: Vineland Adaptive Behaviour (VABS) and Bayley Scales of Infant Development (BSID); specific assessments used in B: Child Behaviour Checklist (CBCL), self-report Social Problem-Solving Inventory–Revised and Sociomoral Reflection Measure, Short Form; specific assessments used in C: CBCL and Strengths & Difficulties questionnaire (SDQ). *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc =$  very low certainty;  $\oplus \oplus \bigcirc \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



FASD

**Figure 24:** Association between fetal alcohol spectrum disorder (FASD) diagnosis and adaptive and social behaviour. A) Direct measures of social cognition and indirect measures of social skills/social problems; B) caregiver reported adaptive behaviour; and C) teacher reported adaptive behaviour. Specific assessments for A: NEuroPSYchological Assessment (NEPSY) theory of mind, Vineland Social Maturity Scale and Children's Interpersonal Problem Solving (ChIPS), teacher report Social Skills Rating Scale (SSRS), and child behaviour checklist (CBCL) and Social Responsiveness Scale (SRS); specific assessments for B: caregiver Vineland Adaptive Behaviour (VABS), Scales of Independent Behaviour Revised (SIB-R), Adaptive Behaviour Assessment System (ABAS); specific assessments for C: teacher VABS. Higher scores indicate better performance except for CBCL caregiver social problems. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  every low certainty;  $\oplus \oplus \bigcirc \bigcirc =$  moderate certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. SMD = Standardised Mean Difference [95% Confidence Interval]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 25:** Association between prenatal alcohol exposure (PAE) or fetal alcohol spectrum disorder (FASD) diagnosis and sensory processing/neurological signs. A) Exposure studies examining caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; and C) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological signs and caregiver reported sensory processing; B) diagnosed studies examining soft neurological sensory Profile (ITSP; odds of <1SD and odds of 'typical scores'); specific assessments for C: Quick Neurological screening Test (QNST-II) and Sensory Processing Measure-Home (SPM; odds of <1SD).

# 4.4.4 Structural and neurological neurodevelopmental outcomes

**Figures 26 to 29** provide an overview of the structural and neurological neurodevelopmental results. See **Supplemental File G** for GRADE summary tables and forest plots, and **Supplemental File D** for a narrative summary of regression data. There were 118 meta-analyses with 1 to 9 studies (Mean = 2.4; Mode = 2) included per meta-analysis. For those outcomes with 5 or more studies included in the meta-analysis (n = 11), 54.5% had high heterogeneity across studies (i.e.,  $l^2 > 75\%$ ). There were no outcomes with  $\geq 10$  studies included in the meta-analysis, and thus funnel plots were not generated (**Supplemental File G**).

# Head circumference

There was a dose-response association between the level of PAE and head circumference at birth (**Figure 26A**). Pooled effect estimates indicated that very heavy PAE was associated with clinically relevant reductions, heavy and moderate PAE were associated with significant reductions, but they were not clinically relevant, and light PAE did not result in reduced head circumference (**Figure 26A**). When head circumference was expressed as a percentile, effect estimates were less precise and only very heavy PAE resulted in a significant reduction (**Figure 26C**). There were fewer studies examining head circumference postnatally and results were more variable, although a dose response was evident when expressed as an OR for small (<10<sup>th</sup> percentile) head circumference (**Figure 26B**). Certainty of this evidence ranged from very low to moderate. Diagnoses of FAS and pFAS were generally associated with lower head circumference at birth and postnatally, with very low to low certainty of this evidence (**Figure 27**).

# Structural brain abnormalities (clinical MRI)

Although many studies provided experimental MRI data on structural brain abnormalities, this was outside the scope of this review as these are not available clinically. Very few studies reported clinically relevant measures. There was only one exposure study available, with confirmed unquantifiable PAE, demonstrating no significantly increased odds of clinically relevant incidental MRI findings (**Figure 28A**). There were only two diagnosed studies available, providing some evidence for FAS/pFAS diagnosis being significantly associated with clinical relevant incidental findings (**Figure 28B**).

Whilst not available clinically, research outcomes for structural quantitative MRI findings have been summarised to provide information regarding changes in brain structure in relation to PAE and FASD diagnosis (**Supplemental File G**). These results may be used to more indirectly support clinical practice.

# Other neurological outcomes

Several other neurological outcomes that are often included in the diagnostic process were examined. However, in all cases, there were only single studies examining a specific exposure level. There was also only one diagnosed study included in this sub-domain. *Hearing loss* was examined across a range of PAE levels, including light and moderate, but was only significantly associated with heavy PAE levels (**Figure 29A**). There was a small increased odds for *cerebral palsy* (**Figure 29B**), but this was only examined in two studies with confirmed unquantifiable PAE (O'Leary et al., 2020; O'Leary & Bower, 2012). Odds for an increased risk for *epilepsy* or neonatal *seizures* were only examined in one study (Sun et al., 2009) across light or moderate PAE across gestation or >1 binge episode (defined as  $\geq$  5 standard drinks on one occasion) at 11-16 weeks gestation. Only the binge exposure was associated with increased odds for these outcomes (**Figure 29C**). Finally, there were only two exposure studies (Falgreen Eriksen et al., 2012; Flanigan et al., 2008) and one diagnosed study (Stromland, 1985) that investigated *visual impairments*. Definitions of visual impairment varied across the available studies, which also contributed to challenges with interpreting available findings. There was poor precision (large 95% Cls) for the effect estimates and overall, no significant associations were found over a range of PAE levels and in individuals diagnosed with FAS (**Figure 29D, E**). All evidence for this sub-domain generally ranged from very low to low certainty, although there was moderate certainty for evidence on the association between PAE and epilepsy or seizures.



**Figure 26:** Association between prenatal alcohol exposure (PAE) and head circumference. A) Head circumference (cm) at birth and post-natally; B) odds ratio of small post-natal head circumference (<10<sup>th</sup> percentile); and C) head circumference as a percentile. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty;  $\bigcirc \bigcirc \bigcirc =$  moderate certainty;  $\bigcirc \bigcirc \bigcirc \bigcirc =$  high certainty. s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. MD = Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4).



Figure 27: Association between fetal alcohol spectrum disorder (FASD) diagnosis and head circumference. A) Head circumference (cm) at birth and postnatally; B) odds ratio of small postnatal head circumference (< 10<sup>th</sup> or 3<sup>rd</sup> percentile); and C) postnatal head circumference as a percentile. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty; s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. MD = Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



Figure 28: Association between prenatal alcohol exposure (PAE) or fetal alcohol spectrum disorder (FASD) diagnosis and structural brain abnormalities from clinical magnetic resonance imaging (MRI). A) Single exposure study examining clinically relevant incidental findings; and B) diagnosed studies reporting clinically relevant incidental findings and agenesis/hypogenesis of the corpus callosum. *Notes:* GRADE Ratings:  $\oplus \bigcirc \bigcirc =$  very low certainty;  $\oplus \oplus \bigcirc \bigcirc =$  low certainty; s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. MD = Mean Difference [95% Confidence Interval (CI)]; OR = Odds Ratio [95% CI]; I<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome; pFAS = partial FAS; ARND = alcohol related neurodevelopmental disorder.



**Figure 29:** Association between prenatal alcohol exposure (PAE) or fetal alcohol syndrome (FAS) diagnosis and other neurological outcomes. Exposure studies reporting A) hearing loss; B) cerebral palsy (CP); C) epilepsy/seizures; and D) impaired vision. E) Single FAS study reporting impaired vision. *Notes:* GRADE Ratings:  $\bigcirc \bigcirc \bigcirc =$  very low certainty;  $\bigcirc \bigcirc \bigcirc =$  low certainty; s = number of studies included in each meta-analysis. n = overall number of participants included in each meta-analysis. OR = Odds Ratio [95% Confidence Interval]; l<sup>2</sup> = indicator of heterogeneity (generated using RevMan 5.4). FAS = fetal alcohol syndrome.

# 5. Limitations and Future Directions

Further research is required across dysmorphology and neurodevelopmental outcomes to enable a comprehensive understanding of the association with PAE across different exposure levels. For dysmorphology outcomes, there was a substantial lack of reporting of normative charts used and variability in the reporting of data, which limited comparisons across available studies. Future research is required to examine the impact of different percentile thresholds and normative charts for palpebral fissure lengths. For functional neurodevelopmental outcomes, there was considerable diversity in the assessment instruments used, as well as reporting methods. Further, there was a paucity of research available that had utilised current clinical assessment tools, with many studies using out-dated versions no longer used in clinical practice. Future research needs to consider how reporting of functional neurodevelopmental outcomes could be more consistent and needs to include up-to-date standardised tools. For structural and neurological outcomes, besides head circumference, there was a general lack of studies available.

Due to the limited data available, the evidence review was unable to examine the potential influence of timing of PAE on the association with offspring outcomes. Given that PAE is more likely to occur exclusively prior to pregnancy recognition (McCormack et al., 2017), this is a critical knowledge gap in the evidence. Also, due to limited data and disparate definitions, the evidence review was unable to examine impacts of 'binge' exposure. Therefore, this review highlights that there are critical gaps in the evidence underlying the currently available diagnostic criteria for FASD, providing many opportunities for future research.

# 6. References

# 6.1 Included studies

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# 7. Appendices

### Appendix A: Search strategies for each database

Database	Search strategy
PubMed	1. prenatal alcohol
Title/Abstract	2. prenatal ethanol
,	3. fetal alcohol
	4. foetal alcohol
	5. fetal ethanol
	6. alcohol exposed
	7. ethanol exposed
	8. 6 OR 7
	9. fetal alcohol spectrum disorder
	10. foetal alcohol spectrum disorder
	11. fetal alcohol syndrome
	12. foetal alcohol syndrome
	13. static encephalopathy
	14. alcohol related birth defect <sup>*1</sup>
	15. alcohol related neurodevelopmental disorder <sup>1</sup>
	16. neurobehav* disorder
	17. 16 AND 1
	18. 16 AND 8
	19. 1 OR 2 OR 3 OR 4 OR 5 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 17 OR
	18 [Alcohol related terms]
	20. prenatal alcohol history
	21. prenatal alcohol level
	22. diagnostic
	23. assessment*
	24. growth
	25. birth weight
	26. birth length
	27. head circumference
	28. physical feature*
	29. facial feature*
	30. dysmorphic feature*
	31. dysmorphology
	32. facial anomal*
	33. facial phenotype
	34. facial criteria
	35. Central nervous system
	36. neurodevelopment*
	37. neuropenav
	38. neuropsychological <sup>2</sup>
	40 cognit*
	40. CUSING 41. intellectual abilit*
	41. Interrectual abilit*
	42. conceptual abilit
	45. executive function
	44. attention 45. boboy*
	45. Delidy
	40. emotional regulation

	47. affect regulation
	48. self regulation <sup>2</sup>
	49. impulse control
	50. impulsivity
	51. hyperactivity
	52. memory
	53. academic achievement
	54. aptitude test
	55. learning
	56. visual spatial <sup>3</sup>
	57. adaptive behavio*
	58. social skills
	59. emotion recognition
	60. social communication
	61. language
	62. sensory
	63. motor
	64. structural brain anomal*
	65. abnormal morphogenesis
	66. neurophysiol*
	67. seizure*
	68. neurolog*
	69. neuroanatomy*
	70. mental health
	71. mental disorder*
	72. mental illness
	73. psychiatric condition <sup><math>+</math></sup>
	74. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32
	OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46
	diagnostic stitutia related terms
	75   19  AND  74
	Example syntax: mental illness[Title/Abstract] <sup>4</sup>
Web of Science	Search terms as per above
Title/Abstract	Example syntax: (TI="mental illness" OR AB="mental illness")
EMBASE	Search terms as per above.
Title/Abstract	Example syntax: 'mental illness':ab,ti
CINAHL	Search terms as per above.
Title/Abstract	Example syntax: TI "mental health" OR AB "mental health"
PsycInfo	Search terms as per above.
Title/Abstract	Example syntax: ti: ("mental illness") OR ab: ("mental illness")
Cochrane Library	Search terms as per above.
Title/Abstract/	Example syntax: (mental illness):ti,ab,kw <sup>4</sup>
Key Words	

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*Note.* <sup>1</sup> Also includes alcohol-related; <sup>2</sup> Also includes self-regulation; <sup>3</sup> Also includes visual-spatial; <sup>4</sup> Entering mental illness results in "mental illness".

### Appendix B: Standardisation of the level of prenatal alcohol exposure across studies

Light PAE, defined as up to 20 g alcohol per week (2 standard drinks per week in Australia), was adapted from

O'Leary et al. (2010). This study described different patterns of alcohol use during pregnancy and defined low exposure in terms of both dose per week (never more than 2 drinks per occasion) and maximum weekly amount (up to 7 drinks in a week). Most papers did not provide both dose and weekly amount so we chose ≤20 g/week to ensure that exposure could never be more than 2 drinks per occasion (i.e., no possibility of a 'binge' exposure, defined as 4 drinks per occasion). The definition for heavy PAE was based on NHMRC Guidelines that recommend no more than 10 standard drinks per week (equivalent to 100 g alcohol), with >10 standard drinks/week defined as 'risky' drinking' (National Health and Medical Research Council (NHMRC), 2020). Therefore, moderate PAE was between the light and heavy levels of exposure. Very heavy PAE was defined by doubling the minimum level for heavy exposure (i.e., >200 g alcohol/week).

In instances where PAE group mean alcohol level was not reported in the study, the PAE category definitions reported in the study methods were used to quantify and classify PAE level using procedures described by Patra et al. (2011). When a range of alcohol intake level was given, the midpoint of the range was used (e.g., 10-20 g per week = 15 g per week). In cases where no upper boundary was provided for the highest category of PAE (e.g., 40+ g per week), three-quarters of the length of the immediate previous category range was added to the lower bound and was used as the amount per week. Where consumption was reported in drinks and not in grams, the grams of pure alcohol per drink (if defined in each article) was used. If the amount of alcohol per standard drink was not defined, conversion was based on geographical location: for Canada 13.6 g, USA 14 g, UK 8 g and for both New Zealand and Australia 10 g pure alcohol per standard drink (see <a href="https://iard.org/science-resources/detail/drinking-guidelines-general-population/">https://iard.org/science-resources/detail/drinking-guidelines-general-population/</a> for definitions of standard drinks). For all other countries without any clear specifications, 12 g pure alcohol was used per standard drink. Where consumption was reported over some other timeframe (e.g., per day or per month), this was converted to weeks. Where multiple study PAE categories were classified into the same exposure level defined in this review, the higher PAE category from the study was used in the analyses.

Study	Description of PAE categories in Methods Section	Standard Drink	PAE Group 1	PAE Group 2	PAE Group 3
Alati et al 2008	Never; <1 glass a week; 1-6 glasses a week; 1 glass+ per day	Not reported; UK-based study (8g)	<1 glass/week = 4 g/week LIGHT Calculation: <8 g/week =	1-6 glasses/week = <b>28 g/week</b> <b>MODERATE</b> Calculation: midpoint of 8 g (1	1 glass+/day = 86 g/week MODERATE <sup>1</sup> Calculation: a) 1 glass/day x 8 g
			midpoint of 1 g-7 g = 4 g/week	glass x 8 g) and 48 g (6 glasses x 8 g) = 28 g/week	<pre>per glass x 7 days = 56 g/week b) ¾ of previous category length = ¾ of 5 drinks [previous category is 1-6 glasses] = ¾ of 40 g [5 glasses x 8 g] = 30 g c) 56 g/week + 30 g/week = 86 g/week</pre>

#### **Example Calculations**

*Note.* <sup>1</sup> Given two of the categories are classified as 'moderate' exposure using our definitions, the higher level was used in the meta-analysis .

## Appendix C: Study characteristics

Study Name	Country	Cohort	Setting	Design	Key sample demographics	Age in years (mean; range)	Gender (% males)	Diagnostic Criteria	Exposure level and/or Diagnosed grouping	Comparator	Covariates/control variables included
Exposure Studies - Quant	ified	•		•				1			
Addila et al. (2021)	Ethiopia	-	Hospitals	Prospective cohort	-	Birth; NR	NR	-	Non-hazardous (light PAE) = 15.38g/w; Hazardous (heavy PAE) = 147.53g/w	Unexposed (No PAE) = 0g/w	NR
Alati et al. (2008)	U.K	ALSPAC	South West England	Prospective cohort	Majority Caucasian	8; NR	50.1	-	<1glass/w (light PAE) = 4g/w; 1- 6glasses/w (moderate PAE) = 28g/w; 1+glasses/day (moderate PAE) = 86g/w	Never (No PAE) = 0g/w	See regression summary table
Alati et al. (2009)	Australia	MUSP	Hospital	Prospective cohort	Majority Caucasian	14; NR	52	-	0-0.5 glasses/day (light PAE) = 17.5g/w; 0.5-1 glass/day (moderate PAE) = 52.5g	Abstainers (No PAE) = 0g/w	-
Alati et al. (2013)	U.К	ALSPAC	South West England	Prospective cohort	Majority Caucasian	11; NR	51.4	-	<1glass/w (light PAE) = 4g/w; 1- 6glasses/w (moderate PAE) = 28g/w; 1+glasses/day (moderate PAE) = 86g/w	Never (No PAE) = 0g/w	See regression summary table
Autti-Ramo and Granstrom (1991a)	Finland	Helsinki	Hospital substance use outpatient clinic	Prospective cohort	-	1.5; NR	52-69	-	Group 1 (heavy PAE) = >140g/w; Group 2 (heavy PAE) = >140g/w; Group 3 (heavy PAE) = >140g/w	Non-exposed (No PAE) = 0g/w	-
Autti-Rämö et al. (1992b)	Finland	Helsinki	Hospital substance use outpatient clinic	Prospective cohort	-	2.25; 2-3	NR	-	Group 1 (heavy PAE) = >140g/w; Group 2 (heavy PAE) = >140g/w; Group 3 (heavy PAE) = >140g/w	Non-exposed (No PAE) = 0g/w	-
Bada et al. (2005)	U.S.	MLS	Hospitals	Prospective cohort	-	Birth; NR	53	-	<1 drink/month (light PAE) = 1.75g/w; 1-3 drinks/month (light PAE) = 7g/w; ≥1 drink/w (light PAE) = 19.25g/w	No alcohol (No PAE) = 0g/w	Adjusted for clinical site, legal & illegal drug use (tobacco, marijuana, cocaine & opiates)
Bakhireva et al. (2018)	U.S.	ENRICH	Prenatal clinics	Prospective cohort	-	Birth; NR & NR; 0.4-0.67	43.6-53.7	-	PAE (moderate PAE) = 86.24g/w	No PAE (No PAE) = 0.02g/w	Matched for SES. Sample included consideration of Medication-assisted therapy (MAT) with opioid agonists for opioid use disorder
Bandoli et al. (2019)	Ukraine	CIFASD	Prenatal clinics	Prospective cohort	-	Birth; NR	NR	-	Trajectory B (light PAE) = 9.8g/w; Trajectory C (moderate PAE) = 60.76g/w; Traectory D (moderate PAE) = 50.96g/w; Trajectory E (very heavy PAE) = 309.68g/w	Trajectory A (No PAE) = 0g/w	See regression summary table
Bandoli et al. (2020)	Ukraine	CIFASD	Prenatal clinics	Prospective cohort	-	1;0-4.3	NR	-	Trajectory B (moderate PAE) = 27.39g/w; Trajectory C (moderate PAE) = 66.28g/w; Trajectory D (moderate PAE) = 96.05g/w; Trajectory E (very heavy PAE) = 367.41g/w (very heavy)	Trajectory A (No PAE) = 0g/w	See regression summary table
Bandoli et al. (2022)	Ukraine	CIFASD	Prenatal clinics	Prospective cohort	-	3.5-4.5	52	-	PAE (moderate PAE) = 45.64g/w	No PAE (No PAE) = NR	-
Bay et al. (2012)	Denmark	LDPS - DNBC	NR	Prospective cohort	-	5.2; NR	51.7	-	1-4 drinks/w (light PAE) = 20g; 5-8 drinks/w (moderate PAE) = 78g/w; 9+ drinks/w (heavy PAE) = 135g/w	0 drinks/w (No PAE) = 0g/w	Adjusted for parental education, maternal IQ, prenatal maternal smoking, maternal age, parity, maternal binge drinking episodes during pregnancy, prenatal & postnatal marital status, postnatal parental smoking, maternal prepregnancy body mass index, child sex, age at testing, health status, hearing & vision on the day of testing, family / home environment, & physical activity (organized sport).

Beauchamp et al. (2020)	U.S.	ENRICH	Antenatal	Prospective cohort	-	Birth; NR	38-54	-	Alcohol (moderate PAE) = 58.80g/w; MOUD+Alcohol (moderate PAE) = 27.44g/w	Control (No PAE) = 0g/w	Matched for SES
Berger et al. (2019)	South Africa	Cape Town LCS	Antenatal	Nested case- control	Cape Coloured	Birth; NR	43.8-68.8	-	Alcohol-exposed (heavy PAE) = 156.80g/w	Typically- developing (No PAE) = 0.06g/w;	-
Brown et al. (1991)	U.S	Atlanta	Hospital	Prospective cohort	Predominantly Black, low SES	5; NR	NR	-	Stopped drinking (very heavy) = 320.88g/w; Continued drinking (very heavy) = 330.96g/w	Never drank (No PAE) = 0g/w	-
Brown et al. (2010)*	U.S	ECLS-B	Nationally representative	Prospective cohort	-	0.75; 0.5-1.8	35.6-61	-	<1 drink/w (light PAE) = 7g/w; 1-3 drinks/w (moderate PAE) = 28g/w; 4+ drinks/w (moderate PAE) = 77g/w	None = 0g/w	See regression summary table
Burden et al. (2011)	Canada	Arctic Monitoring Assessment Program	Hospitals	Nested case- control	Inuit	11.3; 9.8-12.9	42.4	-	Alcohol-exposed (moderate) = 58.80g/w	Control (No PAE) = 0g/w;	
Burden et al. (2005a)*	U.S	Detroit	Hospital clinic	Prospective cohort	African American	7.7; 7.2-8.9	58.5	-	Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Carter et al. (2007)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	0.54; NR & 1; NR	42-61.1	-	Heavy drinkers (heavy PAE) = 196g/w	Abstainers-Light drinkers (No PAE) = 0g/w	See regression summary table
Carter et al. (2012)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	Birth; NR	44.4-60	Hoyme et al. (2005)	Heavy exposure (heavy PAE) = 176.40g/w	Controls (No PAE) = 0g/w;	See regression summary table
Carter et al. (2022)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	Birth; NR & 5; NR	48.3-53.5	-	Heavy exposure (heavy PAE) = 178.60g/w	Controls (No PAE) = 0g;	See regression summary table
Chiaffarino et al. (2006)	Italy	-	Hospital	Case-control	Cases' were SGA and controls were non-SGA	Birth; NR	NR	-	0.5 units/day (moderate PAE) = 42g/w; 1 unit/day (moderate PAE) = 84g/w; 2 units/day (heavy PAE) = 168g/w; 23 units/day (very heavy PAE) = 315g/w	0 units/day (No PAE) = 0g/w;	Adjusted for education, parity & smoking during the third trimester of pregnancy, gestational hypertension, & history of SGA birth
Chiodo et al. (2010)*	U.S	Detroit	Antenatal clinic	Prospective cohort	African American	6.9; NR	49.4-51.6	-	Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Chiodo et al. (2009)*	U.S	Detroit	Antenatal clinic	Prospective cohort	African American	4.42; 3.93-5.63	53.2	-	Continuous measure of average ounces of alcohol per day during pregnancy - M = 63.49g/w (moderate PAE); Range from 0g/w (no PAE – 660.8g/w (very heavy PAE).	-	See regression summary table
Coles et al. (1987)	U.S	Atlanta	Hospital	Prospective cohort	Predominantly Black, low SES	Birth; NR	NR	-	Stopped (very heavy PAE) = 395.92g/w; Continued (very heavy PAE) = 341.04g/w	Never (No PAE) = 0g/w	-
Coles et al. (1991)	U.S.	Atlanta	Hospital	Prospective cohort	Predominantly Black, low SES	Birth; NR & 5.83; NR	44.1	-	Stopped (very heavy PAE) = 320.88g/w; Continued (very heavy PAE) = 330.96g/w	Never (No PAE) = 0g/w	-
Coles et al. (2019)	Ukraine	CIFASD	Prenatal clinics	Nested case- control	-	0.5; NR	47-54.3	-	Alcohol-exposed - full-term (moderate PAE) = 44.30g/w; Alcohol-exposed - pre-term (moderate PAE) = 49.98g/w	Control (full- term and pre- term) = 0g/w	See regression summary table

Coles et al. (2021)	Ukraine	CIFASD	Prenatal clinics	Nested case- control	-	Birth; NR & NR; 3.5-4.5	48.7-54.5	-	Alcohol exposure (heavy PAE) = 124.85g/w	No exposure (no PAE) = 0g/w	-
Day et al. (2013)*	U.S	-	Prenatal clinic	Prospective cohort	57% African American	22.8; 21-26	48	-	0< ADV <1 (moderate PAE) = 49g; ADV ≥1 (heavy PAE) = 150.5g/w	Average daily volume (ADV) of alcohol (No PAE) = 0g/w	See regression summary table
Day et al. (1990)	U.S.	-	Prenatal clinic	Prospective cohort	Low SES	Birth; NR & 0.67; NR	48	-	All other use - <1 drink/day (moderate PAE) = 49g; Heavy use - ≥1 drink/day (heavy PAE) = 150.5g/w	Abstinence (No PAE) = 0g/w;	Birth outcomes: adjusted for maternal height, gestational age, weight gain during pregnancy, cigarette use during pregnancy, race & sex; Postnatal outcomes: adjusted for maternal height, gravidity, gestational age, sex of infant, age of infant
Eckstrand et al. (2012)	U.S	Detroit	Hospital prenatal clinic	Nested case- control	African American	19.55; NR	44.4-90.9	-	Exposed (very heavy PAE) = 218.29g/w	Controls - abstained/low exposure (No PAE) = 7.94g/w;	Matched for age
Faden et al. (1997)	U.S.	NMIHS - live birth sample	Admin data (birth certs) and mail out survey	Prospective cohort	-	Birth; NR	NR	-	<pre>&lt;1 unit/month (light PAE) = 1.75g/w; 1 unit/month (light PAE) = 3.5g/w; 2-3 units/month (light PAE) = 8.75g/w; 1 unit/w (light PAE) = 14g/w; 2 units/w (moderate PAE) = 28g/w; 3-5 units/w (moderate PAE) = 56g/w; 6+ units/w (heavy PAE) = 105g/w</pre>	None (No PAE) = 0g/w	Adjusted for maternal age at delivery, smoking during pregnancy, parity, race, sex of child, mother's body mass index (based on mother's pre-pregnancy weight in kilograms & height in centimetres), mother's height & mother's educational level
Falgreen Eriksen et al. (2012)	Denmark	LDPS - DNBC	Telephone interviews	Prospective cohort		Birth; NR & 5.2; NR	52	-	1-4 drinks/w (light PAE) = 12g/w; 5- 8 drinks/w (moderate PAE) = 60g/w; ≥9 drinks/w (heavy PAE) = 120g/w	0 drinks/w (No PAE) = 0g/w	IQ/Cognition outcomes: Adjusted for parental education, maternal IQ, prenatal maternal smoking and binge drinking, maternal age, parity, prenatal and postnatal marital status, postnatal parental smoking, maternal pre-pregnancy BMI, the child's gender and age, health status, hearing and vision on the day of testing, family/home environment, and tester.
Flanigan et al. (2008)	Chile	NICHD	Community health clinics	Nested case- control	-	5.95; 4-9	53	-	Heavy drinkers (Very Heavy PAE) = 487.2g/w	Non-drinkers (No PAE) = 0g/w	Matched for maternal age, parity, & gestational age
Forrest et al. (1991)*	Scotland	Sulaiman 1988	Antenatal & follow-up clinic	Prospective cohort	-	1.5; NR	?	-	1-49g/w (moderate PAE) = 25g/w; 50-99g/w (moderate PAE) = 74.5g/w; ≥100g/w (heavy PAE) = 136.75g/w	-	See regression summary table
Fraser et al. (2012)*	Canada	Jacobson 2008	Prenatal clinic	Prospective cohort	Inuit	Birth; NR & 0.5; NR	57	-	Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Goldschmidt et al. (1996)	U.S	Maternal Health Practices and Child Developmen t Project	Hospital prenatal clinic	Prospective cohort	49% Caucasian; 51% African American	6; NR	NR	-	Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Greene et al. (1990)*	U.S	Cleveland	Hospital prenatal clinic	Prospective cohort	-	2.05; NR & 3.08; NR	51	-	Continuous measure of average ounces of alcohol per day during pregnancy – M = 13.86g/w (light PAE); Range – 0g/w to 414.75g/w (very heavy PAE)	-	See regression summary table
Greene et al. (1991a)*	U.S	Cleveland	Hospital prenatal clinic	Prospective cohort	-	Birth; NR & 4; NR	51	-	Continuous measure of average ounces of alcohol per day during pregnancy – M = 13.86g/w (light PAE); Range – 0g/w to 414.75g/w (very heavy PAE)	-	See regression summary table

Halliday et al. (2017)	Australia	AQUA	Hospitals	Prospective cohort	-	2; NR	NR	-	Low in T1-abstinent in T2&T3 (moderate PAE) = 35.5g/w; Moderate/High in T1-abstinent in T2&T3 (moderate PAE) = 76.13g/w	No (No PAE) = Og/w	Sensory & infant behaviour outcomes: adjusted for multiple covariates - varied across outcomes.
Hannigan et al. (2010)*	U.S	Detroit	Hospital prenatal clinic	Prospective cohort	African American	14.7; 13.3-17.8	50.7	-	Continuous measure of average ounces of alcohol per day during pregnancy – M = 5.95-77.35g/w (antenatal – retrospective report)	-	See regression summary table
Holzman et al. (1995)	U.S.	NBH	Hospitals	Prospective cohort	Infants < 31 weeks' gestation and< 2000g	Birth; NR	37-54	-	Moderate use (moderate PAE) = 49g/w; Heavy use (Heavy PAE) = 150.5g/w	Abstainers (No PAE)= 0g/w;	Adjusted for gender & multiple births status
Hutchinson et al. (2019)	Australia	Triple B	Antenatal clinics	Prospective cohort	Majority high SES	1; 0.66-1.8	-	-	[Trimester 1a] Low (light PAE) = 17.50g/w; Moderate (moderate PAE) = 27.50g/w; Heavy (heavy PAE) = 181.16g/w	Abstinent (No PAE) = 0g/w	Physical size & structural neuro outcomes: no adjustments. Motor outcome: adjusted for Age at birth, Education, SEIFA, State of residence, Country of birth, Single parent household, Aboriginal & Torres Strait Isl&er status, Native language, & infant- related variables (Gestational age).
Jacobson et al. (1993b)*	U.S	Detroit	Hospital prenatal clinic	Prospective cohort	African American, low SES	0.54; NR & 1; NR	57.8	-	Continuous measure of average ounces of alcohol per day during pregnancy.	-	See regression summary table
Jacobson et al. (1994a)	U.S.	Detroit	Hospital prenatal clinic	Prospective cohort	African American	6.5; NR	58.3	-	0.01-0.24ozAA/day (moderate PAE) = 24.50g/w; 0.25-0.49ozAA/day (moderate PAE) = 72.52g; 0.50- 0.99ozAA/day (heavy PAE) = 145.99; 1.00-1.99ozAA/day (very heavy PAE) = 293.02g; 2.0ozAA/day (very heavy PAE) = 537.60g/w	0.00ozAA/day (No PAE) = 0g/w	See regression summary table
						Birth; NR & 0.54; NR &					
Jacobson et al. (1998)*	U.S	Detroit	Hospital prenatal clinic	Prospective cohort	African American, Iow SES	1; NR & 1.08; NR	NR	-	Continuous measure of average ounces of alcohol per day during pregnancy.	-	See regression summary table
Jacobson et al. (2004)*	U.S	Detroit	Hospital prenatal clinic	Prospective cohort	African American, Iow SES	7.7; 7.2-8.9	58.4	-	Continuous measure of average ounces of alcohol per day during pregnancy.	-	See regression summary table
Jacobson et al. (2017)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	17.8 days; 6- 40days	41.8	Hoyme et al. (2005)	PAE (moderate PAE) = 46.78g/w	Healthy Controls (No PAE) = 0.01g/w	See regression summary table
Jaddoe et al. (2007)	Netherlands	Generation R	Ultrasound appoitments	Prospective cohort	-	Birth; NR	NR	-	<1 drink/w (light PAE) = 5g/w; 1-6 drinks/w (moderae PAE) = 42g/w; ≥1 drink/day (heavy PAE) = 129g/w	No alcohol consumption (No PAE) = 0g/w	Adjusted for maternal body mass index, smoking, educational level, height, ethnicity, parity & age & infant gender; birth weight & low birth weight models also controlled for gestational age
Kelly et al. (2009)	UK	Millenium	Home visits	Prospective cohort	-	Birth; NR	50.2-54.6	-	Light (light PAE) = 12g/w; Moderate (moderate PAE) = 36g/w; Heavy/binge (moderate PAE) = 74g/w	Never (No PAE) = 0g/w	-
Kesmodel et al. (2012)	Denmark	LDPS- DNBC	Antenatal	Prospective cohort	-	5.22; 5-5.34	52	-	1-4 drinks/w (light PAE) = 20g; 5-8 drinks/w (moderate PAE) = 78g/w; 9+ drinks/w (heavy PAE) = 135g/w	0 drinks/w (No PAE) = 0g/w	Adjusted for rental education, maternal IQ, prenatal maternal smoking, the child's gender & age at testing & tester, parity, maternal marital status, age, BMI, prenatal maternal average number of drinks per w, home environment, postnatal parental smoking, health status, hearing & vision abilities.
Korkman et al. (1998)	Finland	-	Hospital substance use	Prospective cohort	-	NR; 5-9	55.5	-	Group 1 (heavy PAE) = >140g/w; Group 2 (heavy PAE) = >140g/w; Group 3 (heavy PAE) = >140g/w	Non- exposed/Abstain	-

			outpatient clinic							ers (No PAE) = 0g/w	
Kuehn et al. (2012)	Chile	NICHD	Community health clinic	Nested case- control	-	Birth; NR	47.6	-	Exposed (very heavy PAE) = 445.63g/w	Unexposed (No PAE) = 0g/w	Adjusted for maternal age, education, parity, reliability of mother's report of alcohol use during pregnancy, & age at which mother started drinking alcohol.
Larroque and Kaminski (1998)*	France	-	Hospital	Prospective cohort	-	4.64; NR	NR	-	0.1-0.49oz/day (moderate PAE) = 58.54g/w; 0.5-0.99oz/day (heavy PAE) = 147.84g/w; 1.0-1.49oz/day (very heavy PAE) = 247.07g/w; 1.5- 2.49oz.day (very heavy PAE) = 395.90g/w; >=2.5oz/day (very heavy PAE) = 642.97g/w	Ooz/day (No PAE) = 0g/w	IQ outcomes: Adjusted for birth order, maternal level of education, present maternal employment, family status, score of family stimulation, gender, age of the child at examination & examiner; Physical size outcomes: birth order, maternal level of education, family status, present maternal employment, gender, age of the child at examination, & mother's height.
Lazzaroni et al. (1993)	Italy	IPAGI	Hospitals	Prospective cohort	-	Birth; NR	60.3	-	1-10g/day (moderate PAE) = 38.5g/w; 11-20g/day (heavy PAE) = 108.5g/w; >20g/day (heavy PAE) = 187.25g/w	Abstainers (No PAE) = 0g/w	LBW outcome: Adjusted for mother's age, sex & gestational age
Lees et al. (2020)	U.S.	ABCD Study	Largely school- based	Nested case- control	-	Birth; NR & NR; 9-10.9	~51	-	Stable-light (light PAE) = 15.4g/w; Heavy-reducer (moderate PAE) = 74.48g/w	No PAE (No PAE) = 0g/w	See regression summary table
Little et al. (1990)	U.S.	MANDATE	Hospital	Nested case- control	-	Birth; NR	NR	-	Drinkers (very heavy PAE) = 392g+/w	Nondrinker (No PAE) = 0g/w	-
Long and Lebel (2022)	U.S	ABCD Study	Largely school- based	Nested case- control	-	9.86; NR	47.7	-	PAE (light PAE) = 14g/w	Unexposed (No PAE) = 0g/w	Matched for age, smoking, other drugs, socioeconomic factors, & sex
Lumley et al. (1985)	Australia	-	Hospital perinatal data	Retrospectiv e cohort	-	Birth; NR	NR		3-6glasses/w (moderate PAE) = 45g/w; ≥2glasses/day (heavy PAE) = 162.5g/w	None (No PAE) = 0g/w	-
Lundsberg et al. (1997)	U.S.	-	Hospital	Prospective cohort	-	Birth; NR	49.8	-	[Month 1 data] ≤0.102AA/day (light PAE) = 9.8g/w; 0.10-<0.25ozAA/day (moderate PAE) = 33.32g/w; ≥0.25- 1.00ozAA/day (heavy PAE) = 122.64g/w; >1.00ozAA/day (very heavy PAE) = 308.28g/w	Abstinent (No PAE) = 0g/w;	Adjusted for smoking in month 7, height, weight, ethnicity, infant sex, parity, coffee use in month 7, exercise in third trimester, employment, bleeding during pregnancy, high blood pressure, pre- eclampsia/eclampsia, anomalies, & placental problems.
Lundsberg et al. (2015)	U.S.	-	Obstetric & prenatal clinics	Prospective cohort	-	Birth; NR	NR	-	<0.10oz/day (light PAE) = 9.8g/w; 0.10~0.25oz/day (moderate PAE) = 33.32g/w; 20.25oz/day (moderate PAE) = 69.72g/w	0oz/d = 0g/w;	Adjusted for parity, age, ethnicity, study cohort, height, marital status, smoking, exercise (before/during pregnancy), multivitamin use, preterm labor, hypertension, & anomalies
Maher et al. (2022)	New Zealand, Australia, Ireland & United Kingdom	SCOPE- BASELINE	Multi-site	Prospective cohort	International cohort	5; NR	50.3	-	Occasional-Low (moderate PAE) = 32g/w; Moderate-Heavy (heavy PAE) = 167g/w	Abstinent (No PAE) = 0g/w	-
Marbury et al. (1983)	U.S.	-	Hospital	Prospective cohort	-	Birth; NR	NR		1-2 drinks/w (light PAE) = 21g/w; 3- 6 drinks/w (moderate PAE) = 63g/w; 7-13 drinks/w (heavy PAE) = 140g/w; 14+drinks/w (very heavy PAE) = 259g/w	0 drinks/w (No PAE) = 0g/w	Maternal age. marital status, race, education, smoking during pregnancy, parity, previous fetal death, & previous induced abortion.
						Birth; NR & 0.5; NR &					
Marianian et al. (2020)	Russia	-	Perinatal centre	Case-control	-	1; NR	NR	-	Group 2 (light PAE) = 0.97g/w	Group 1 (No PAE) = 0g/w	-

Mariscal et al. (2006)	Spain	-	Hospital	Case-control	-	Birth; NR	NR	-	1-5.9g/day (moderate PAE) = 27.6g/w; 6-11.9g/day (moderate PAE) = 62.65g/w; ≥12g/d (heavy PAE) = 114.98g/w	Nondrinkers (No PAE) = 0g/w	Adjusted for Kessner index, social class, employment outside home, previous low birth weight, hypertensio diabetes, tobacco consumption, & smoker partners
McCarthy et al. (2013)	NZ, Aus, Ireland & UK	SCOPE	Multi-site	Prospective cohort	International cohort	Birth; NR	NR	-	Occasional-Low (moderate PAE)= 32g/w; Moderate-Heavy (heavy PAE) = 167g/w	Abstinent (No PAE) = 0g/w	Adjusted for maternal age, smoking, education, ethnicity, body mass index, neonatal sex, marital stat family income, & drug use in pregnancy. All analysocioeconomic statuswere adjusted for potentii clustering effect of study centers. Birth weight model were also adjusted for gestational age at delivery.
McCormack et al. (2018)	Australia	Triple B	Antenatal clinics	Prospective cohort	Majority high SES	12.05 months; 11-16 months	NR	-	Low (moderate PAE) = 40g/w; Moderate (moderate) = 50g/w; Heavy (heavy PAE) = 110g/w	Abstainers (No PAE) = 0g/w	See regression summary table
McDonald et al. (1992)	Canada	-	Hospitals	Prospective cohort	Socioeconomic status were LBW	Birth; NR	NR	-	1-2 drinks/w (light PAE) = 20.25g/w; 3-6 drinks/w (moderate PAE) = 60.75g/w; 7-20 drinks/w (heavy PAE) = 182.25g/w; 21+drinks/w (very heavy PAE) = 415.13g/w	None (No PAE) = 0g/w	Adjusted for age, pregnancy order, previous spontaneous abortion, previous low birth weight info prepregnancy weight, ethnic group, education, employment, coffee consumption
Mills et al. (1984)	U.S.	-	Hospital	Retrospectiv e cohort		Birth; NR	NR	-	<pre>&lt;1 drink/day (moderate PAE) = 52.5g/w; 1-2 drinks/day (heavy PAE) = 147g/w; 3-5 drinks/day (very heavy PAE) = 392g/w; ≥6 drinks/day (very heavy PAE) = 735g/w</pre>	Nondrinkders (No PAE) = 0g/w	Adjusted for mother's age, race, education, marital status, weight-for-height percentile, smoking, parity, previous spontaneous abortions, hypertension, preeclampsia, length of gestation, & sex of infant
Mitchell et al. (2020)	UK	Millennium	Home visits	Prospective cohort	-	7; NR	49.4	-	Light (moderate PAE) = 40g/w; Moderate (moderate PAE) = 88g/w; Heavy (heavy PAE) = 148g/w	No (No PAE) = 0g/w	Adjusted for gender, gestational age at delivery, maternal age, paternal age, maternalsmoking, mate pre-pregnancy BMI, household income, maternal education, ethnicity, marital status
Miyake et al. (2014)	Japan	комсня	Hospitals	Prospective cohort	-	Birth; NR	48.7	-	<1.0g/d (light PAE) = 3.5g/w; ≥1.0g/d (light PAE) = 10.75g/w	None (No PAE) = 0g/w	Adjusted for maternal age; region of residence; num of children; family structure; maternal education; maternal employment; body mass index; maternal smoking during pregnancy; gestational age; & baby's gender.
Niclasen et al. (2014)	Denmark	DNBC	Antenatal	Prospective cohort	-	Birth; NR	51	-	>0-5 units (light PAE) = 0.84g/w; >5- 15 units (light PAE) = 3g/w; >15-45 units (light PAE) = 8.52g/w; >45-90 units (light PAE) = 19.44g/w; >90 units (moderate PAE) = 42.24g/w	0 units (No PAE) = 0g/w;	-
Nykjaer et al. (2014)	UK	CARE	Hospital	Prospective cohort	-	Birth; NR	NR	-	[Trimester 1 data] ≤2 units/w (light PAE) = 6.4g/w; >2 units/w (moderate PAE) = 57.6g/w	Nondrinker (No PAE) = 0g/w	Adjusted for maternal pre-pregnancy weight, height age, parity, ethnicity, salivary cotinine levels, caffein intake, education, energy intake, gestation & baby's
O'Callaghan et al. (2007)	Australia	MUSP	Hospital	Prospective cohort	Majority Caucasian	13.9; 12.5-15.5	NR	-	>0 to <1/2 glass/day (moderate PAE) = 25.48g/w ; 1/2 to <1glass/day (moderate PAE) = 73.36g/w; >=1glass/day (heavy PAE) = 134.68g/w	Nil (No PAE) = 0g/w	Adjusted for maternal BMI <18.5, cigarette smoking early & late pregnancy, & social risk score (low mate education, maternal age <19 years, single parent sta or low income in pregnancy or at 14 years).
O'Leary et al. (2013)	Australia	RASCALS	Postal survey & data linkage	Prospective cohort	Non-Indigenous Western Australians	NR; 8-9	NR	-	Low (moderate PAE) = 35g/w; Moderate (moderate PAE) = 50g/w; Heavy (heavy PAE) = 110g/w	Abstinent - never (No PAE) = 0g/w	Adjusted for maternal age, education, marital status ethnicity, parity, illicit &/or tranquilizer drug use, smoking, income, & languages spoken at home.
O'Leary et al. (2009a)	Australia	RASCALS	Postal survey & data linkage	Prospective cohort	-	Birth; NR	NR	-	[Trimester 1] Low (light PAE) = 6.2g/w; Moderate (light PAE) = 16.6g/w; Heavy (heavy PAE) = 192.5g/w	Abstinent (No PAE) = 0g/w	Adjusted for maternal age, smoking, ethnicity, marit status, parity, drug use, income, maternal medical conditions, procedures, & treatments during pregna & pregnancy complications.

O'Leary, Nassar, et al. (2010)	Australia	RASCALS	Postal survey & data linkage	Prospective cohort	-	2; NR & 5; NR & 8; NR	NR	-	[Trimester 1] Low (light PAE) = 2.5g/w; Moderate (light PAE) = 9g/w ; Heavy (heavy PAE) = 120g/w	Abstinent (No PAE) = 0g/w	Adjusted for maternal age, ethnicity, parity, marital status, income, smoking & illicit drug use (including tranquillizers & sleeping tablets) during pregnancy; & for postnatal depression & variables collected at each follow-up: marital status, income, maternal depression, anxiety & stress, McMaster family functioning, parenting scales, tension in family due to alcohol misuse & age of completion of CBCL.
O'Leary et al. (2009b)	Australia	RASCALS	Postal survey & data linkage	Prospective cohort	-	2; NR	NR	-	[Trimester 1] Low (light PAE) = 6.1g/w; Moderate (light PAE) = 16.5g/w; Heavy (heavy PAE) = 161g/w; Mod-Heavy (moderate PAE) = 88.75g/w	Abstinent (No PAE) = 0g/w	Adjusted for McMaster's' family functioning, parenting scale, partner present, maternal depression, anxiety, & stress; & Prenatal factors: maternal age at delivery, income, marital status, parity, education, smoking, use of tranquilizers, & illicit drug use.
Oberlander et al. (2010)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	Birth; NR	28.6-64.3	-	Exposed (heavy PAE) = 156.80g/w	Control (No PAE) = 1.96g/w	-
Olsen et al. (1991)	Denmark	-	Midwife centres	Prospective cohort	-	Birth; NR	NR	-	1-29g/w (light PAE) = 15g; 30-59g/w (moderate PAE) = 44.5g; 60-89g/w (moderate PAE) = 74.5g/w; 90- 119g/w (heavy PAE) = 104.5g/w; 120+g/w (heavy PAE) = 141.75g/w	No PAE (No PAE) = 0g/w	Adjusted for smoking, age, school education & parity
Popova et al. (2021)	Canada	BC Perinatal Registry	Admin data	Case-control	-	Birth; NR	50.1-5.3	ICD-10	Alcohol use (moderate PAE) = 46.24g/w	No alcohol use (No PAE) = 0g/w	Physical Size outcomes: Adjusted for maternal age, maternal smoking status, any maternal substance use, parity, prior neonatal deaths, prior stillbirth & prior low birthweight newborn,maternal history of any mental illness & the number of antenatal visits
Primatesta et al. (1993)	UK & Italy	-	Hospitals	Prospective cohort	-	Birth; NR	NR	-	1-137g (moderate PAE) = 69g/w; 138-276g (very heavy PAE) = 207g/w (very heavy); 277rg (very heavy PAE) = 380.5g/w	Abstinent (No PAE) = 0g/w	-
Salihu et al. (2011)	U.S.	Missouri linked data	Admin data	Nested case control	-	Birth; NR	NR	-	1-2 drinks/w (light PAE) = 21g/w; 3- 4 drinks/w (moderate PAE) = 49g; >5 drinks/w (heavy PAE) = 80.5g/w	Nondrinker (No PAE) = 0g/w	Adjusted for maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, maternal height, gender of the infant, & year of birth.
Sayal et al. (2007)	U.K	ALSPAC	Southwest England	Prospective cohort	White-European	6.75; NR & NR; 7.75-9	62.2 & 73.3	-	< 1 glass/w (light PAE) = 4g/w; ≥1 glass/w (light PAE) = 12.5g	Never (No PAE) = 0g/w	Adjusted for gender, smoking, cannabis use & use of illicit drugs in the first trimester; highest level of maternal education; home ownership; marital status; parity; maternal age group; high EPDS score; child ethnicity; gestational age group; & birth weight.
Sayal et al. (2013)	U.K	ALSPAC	Southwest England	Prospective cohort	White-European	Birth; NR & 11; NR	~50	-	< 1 glass/w (light PAE) = 4g/w; ≥1 glass/w (light PAE) = 12.5g	Never (No PAE) = 0g/w	Functional neuro outcomes: Adjusted for maternal age, parity, highest level of maternal education, daily frequency of smoking, use of cannabis &/or other illicit drugs during the first trimester, home ownership, whether currently married, high scores (>12) on the Edinburgh Postnatal Depression Scale, & child gestational age, birth weight & gender.
Shu et al. (1995)	U.S.	-	Prenatal clinics	Prospective cohort	-	Birth; NR	NR	-	<1drink/w (light PAE) = 7.0g/w; <2 drinks/w (light PAE) = 19.6g/w	None (No PAE) = 0g/w	Gestational age, parity, smoking, income
Skogerbo et al. (2012)	Denmark	LDPS-DNBC	Antenatal	Prospective cohort	-	5; NR	NR	-	1-4 drinks/w (light PAE) = 20g/w; 5- 8 drinks/w (moderate PAE) = 78g/w; 9+ drinks/w (heavy PAE) = 135g/w	0 drinks/w (No PAE) = 0g/w	Adjusted for maternal smoking, binge drinking, maternal age, parity, prenatal & postnatal marital status, postnatal parental smoking, maternal pre-pregnancy BMI, gender of child, age at testing, health status on the day of testing, & family/home environment.
Skogerbo et al. (2013)	Denmark	LDPS-DNBC	Antenatal	Prospective cohort	-	5; NR	NR	-	1-4 drinks/w (moderate PAE) = 30g/w; 5+ drinks/w (moderate PAE) = 87g/w	0 drinks/w (No PAE) = 0g/w	Adjusted for all potential confounding factors: parental education, maternal IQ, prenatal maternal smoking, child's age at testing, child's gender, binge drinking, maternal age, parity, maternal marital status, family home environment, postnatal parental smoking,

											prepregnancy maternal body mass index (BMI), & the child's health status
Sood et al. (2001)	U.S	-	Maternity clinic	Prospective cohort	African American	6.9; 6-7	49.6-53.0	-	Low (moderate PAE) = 29.4g/w; Moderate/Heavy (moderate PAE) = 98.84g/w	No PAE (No PAE) = 0g/w	See regression summary table
Sood et al. (2005)	U.S.	-	Maternity clinic	Nested case- control	African American	Birth; NR	~50	-	PAE with no prenatal cocaine (light) = 19.6g/w; PAE with any prenatal cocaine (moderate PAE) = 58.8g/w	No PAE - both with no and any prenatal cocaine (No PAE)= 0g/w	
Streissguth et al. (1980)*	U.S	Seattle (FAS Follow-up)	Antenatal & follow-up clinic	Prospective cohort	-	8 months; NR	NR	-	Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Streissguth et al. (1984)*	U.S	Seattle (FAS Follow-up)	Antenatal & follow-up clinic	Prospective cohort	-	4.25; NR	NR	-	Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Sun et al. (2009)	Denmark	DNBC	Antenatal	Prospective cohort	-	NR; NR	NR	-	0.5-1-5drinks/w (light PAE) = 12g/w; 2-3.5drinks/w (moderate PAE) = 33g/w; >=4 drinks/w (moderate PAE) = 61.5g/w	0 drinks/w (No PAE) = 0g/w	Adjusted for gestational age at birth, maternal age, parity, time to pregnancy, household socio-occupational status, smoking status at time of first interview & maternal history of epilepsy. For binge drinking, also adjusted for average alcohol consumption.
Taylor et al. (2015)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	NR; 36-44 weeks	55	-	Heavy drinkers (very heavy PAE) = 329.28g/w	Controls (No PAE) = 1.96g/w	See regression summary table
Underbjerg et al. (2012)	Denmark	LDPS-DNBC	Antenatal	Prospective cohort	-	5; NR	NR	-	1-4 drinks/w (light PAE) = 12g/w; 5- 8 drinks/w (moderate PAE) = 60g/w; ≥9 drinks/w (heavy PAE) = 120g/w	0 drinks/w (No PAE) = 0g/w	Adjusted for parental education, maternal IQ, prenatal maternal smoking & binge drinking, maternal age, parity, prenatal & postnatal marital status, postnatal parental smoking, maternal pre-pregnancy BMI, the child's gender & age, health status, hearing & vision on the day of testing, family/home environment, & tester.
Verkerk et al. (1993)*	Netherlands	-	Antenatal	Prospective cohort	-	Birth; NR	NR		1-50g/w = 25.5g/w (moderate); 51- 120g/w = 85.5g/w (moderate); >120g/w = 171.75g/w (heavy)	Abstainer = 0g/w	See regression summary table
Virji (1991)	U.S.	NNS	Antenatal	Prospective cohort	White respondents only	Birth; NR	NR	-	Light (light PAE) = 8.5g/w; Moderate = (heavy PAE) = 119g/w; Heavy (very heavy PAE) = 391g/w	None (No PAE) = 0g/w	See regression summary table
Whitehead and Lipscomb (2003)	U.S	PRAMS	Admin data and mail out survey	Retrospectiv e cohort	-	Birth; NR	NR	-	Light (light PAE) = 21.5g/w; Moderate (heavy PAE) = 119g/w; Heavy (very heavy PAE) = 290.5g/w	Nondrinker (No PAE) = 0g/w	Adjusted for number of cigarettes smoked per day during the last 3 months of pregnancy, income from public assistance, maternal age, maternal education, marital status, prepregnancy weight, & maternal state of residence
Willford et al. (2006)*	U.S	Maternal Health Practices and Child Developmen t Project	Hospital prenatal clinic	Prospective cohort	-	10.5; NR	NR		Continuous measure of average ounces of alcohol per day during pregnancy	-	See regression summary table
Windham et al. (1995)	U.S.	-	Hospitals	Prospective cohort		Birth; NR	NR	-	0.1-2 drinks/w (light PAE) = 14.7g/w; 3-5 drinks/w (moderate PAE) = 56g/w; 6+ drinks/w (heavy PAE) = 105g/w	None (No PAE) = 0g/w	Adjusted for smoking, caffeine, race, insurance coverage, & hypertension

Yang et al. (2001)	U.S.	Monroe County	Admin data	Retrospectiv e cohort	'Cases' were IUGR	Birth; NR	NR	-	<3 drinks/w (light PAE) = 21g/w; 3- 13 drinks/w (heavy PAE) = 112g/w; 14+ drinks/w (very heavy PAE) = 301g/w	None (No PAE) = 0g/w	Adjusted for maternal age, weight gain during pregnancy, educational attainment, race, number of cigarettes smoked/day.
Zuccolo et al. (2016)	Norway	МоВа	Questionnaire & data linkage	Prospective cohort	-	Birth; NR	NR	-	<1 units/w (light PAE) = 7g/w; 1-2 units/w (light PAE) = 21g/w; 3-4 units/w (moderate PAE) = 49g/w; 5+ units/w (moderate PAE) = 80.5g/w	Nondrinker (No PAE) = 0g/w	Adjusted for year of birth, folic acid use around conception, whether the pregnancy was planned, maternal diabetes (pre-conception diabetes or gestational diabetes), parity, ethnicity, financial strain, and maternal and paternal age, height, body-mass index (BMI), gross income, education, and smoking
Exposure Studies - Confirm	ned unquantifiab	le or No/Any PAE									
Aghamohammadi- Sereshki et al. (2022)	Canada	-	Community- based	Case-control	-	10.02; NR	42.5	-	PAE (confirmed-unquantifiable)	Unexposed (No PAE) = NR	Matched for age, gender, annual household income & maternal education
Bjorkquist et al. (2010)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	11.4;8-16	48-50	NR	Alcohol-exposed (confirmed- unquantifiable) = NR	Control (No PAE) = NR	Matched for age, race, socioeconomic status, & sex
Borges et al. (1993)	Mexico	-	Household survey	Nested case- control	Socioeconomic status were LBW and/or preterm; LBW NR	Birth; NR	NR	-	Alcohol - yes (Any PAE) = NR	Alcohol - No (No PAE) = NR	Matched for age and community. Adjusted for smoking
Cardenas et al. (2014)	U.S	San Diego	FASD clinic	Nested case- control	-	13; NR	70	NR	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-
Chandran et al. (2021)	India	-	Hospital	Case-control	Low socioeconomic status	9.5 ;6-16	43.1	-	Exposed (confirmed-unquantifiable) = NR	Non-exposed (No PAE) = NR	Matched for age, sex & education
Cho et al. (2021)	Japan	JECS	Health clinics	Prospective cohort	-	Birth; NR	NR	-	Alcohol drinkers - yes (Any PAE) = NR	Alcohol drinkers - no (No PAE) = NR	Adjusted to education, parity & smoking during the third trimester, gestational hypertension, history of SGA birth
Crocker et al. (2009)	U.S	San Diego	FASD clinic	Nested case- control	-	10.14; 6-13	61.9	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	Matched for age, sex, socioeconomic status (SES) & race/ethnicity
Crocker et al. (2015)	U.S	San Diego	FASD clinic	Nested case- control	-	10.05; 7-12	58.9	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Donald et al. (2016)	South Africa	DCHS	Antenatal	Nested case- control	-	NR; 2-4 weeks	50	-	Alcohol-exposed (confirmed- unquantifiable)	Control (No PAE) = NR	Structural neuro outcome: Corrected for age, gender, ethnicity, maternal smoking status & total gray matter volume
Doyle et al. (2018)	U.S	CIFASD III	Multi-site	Case-control	-	13.2; 10-16	51.6	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Doyle et al. (2019a)	U.S	CIFASD II	Multi-site	Case-control	-	12.3; 8-16	60.6	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
						Birth; NR &					
Furtado and Roriz (2016)	Brazil	Gesta- Alcohol Study	Obstetric clinic	Nested case- control	-	NR; 6-7 & NR; 11-12	57.1	-	PAE (Any PAE)	Non-PAE (No PAE) = NR	-
Gautam et al. (2015)	U.S. & South Africa	CIFASD	Multi-site	Case-control	-	12.3; 7.1-15.9	55.3	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Glass et al. (2013)	U.S	CIFASD	Multi-site	Nested case- control	-	12.28; 8-16	50.5	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Glass et al. (2014)	U.S	CIFASD I - San Diego	FASD clinic	Nested case- control	Majority Caucasian	12.24; 7-18	60.6	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-

Glass et al. (2015)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	12.47; 8-16	49.4	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Glass et al. (2017)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	12.69; 8-16	60.1	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Gao et al. (2019)	U.S	-	NR	Case-control	-	15.8; NR	62.5	-	PAE (Any PAE)	Healthy Controls (No PAE) = NR	-
Golden et al. (1982)	U.S.	-	NR	Case-control	-	Birth; NR & 1; 0.5-1.67	NR	-	Study group (confirmed- unquantifiable)	Matched control (No PAE) = NR	Matched for gestational age, sex & race
Gomez et al. (2022)	Canada	-	Diagnostic clinic	Case-control	-	10.35; 7.1-15.9	58.06	-	PAE (confirmed-unquantifiable)	Unexposed controls (No PAE) = NR	-
Graham et al. (2013)	U.S.	CIFASD	Multi-site	Case-control	-	~12; 8-16	59.5	CIFASD	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	Matched for age, race, ethnicity & sex
Grisso et al. (1984)	U.K	-	Hospitals	Prospective cohort	-	Birth; NR	NR	-	Everyday (confirmed- unquantifiable)	Not at all (No PAE) = NR	-
Gross et al. (2018)	U.S	CIFASD III	Multi-site	Nested case- control	-	13.25; 10-16	54.9	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Hendricks et al. (2020)	South Africa	DCHS	Health clinics	Prospective cohort	Low SES	0.5 & 2	55	-	Alcohol-exposed (confirmed- unquantifiable)	Control (No PAE) = NR	Adjusted for SES, smoking, PTSD & depression
Hendrickson et al. (2017)	U.S.	CIFASD	Multi-site	Case-control	-	~13; 9-16	47-58	CIFASD	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Ichikawa et al. (2018)*	Japan	J-SHINE 2012-2013	Household survey	Prospective cohort	-	9.49; 2-18	50.2	-	Unable to quantify to grams/w.	-	See regression summary table
Infante et al. (2017)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	13.7; 10-16	56.75	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE) = NR	-
Jackson et al. (2007)	South Africa	-	Hospital	Case control	11-14% Black African; 'cases' were LBW (<2500g) controls normal weight	Birth; NR	NR	-	Alcohol ingestion - yes (Any PAE)	Alcohol ingestion - no (No PAE) = NR	Adjusted for smoking, first antenatal maternal weight, primary school only, number of antenatal visits
Kyllerman et al. (1985)	Sweeden	-	Substance use clinics	Case-control	-	Birth; NR & ~6; NR	NR	-	Alcoholic (confirmed- unquantifiable)	Matched controls (No PAE)	Matched for sex, age, birthweight, gestational age & living area
Lebel et al. (2012)	U.S. & South Africa	CIFASD	Multi-site	Case-control	South Africa cohort - Cape Coloured	12.4; 5.7-15.9	55.6	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE)	-
Lee et al. (2004)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian & middle class	11.5; 9-16.9	43.3	-	Alcohol-exposed (confirmed- unquantifiable)	Non-exposed (No PAE)	Matched for age, sex, social status, & ethnicity
Long et al. (2019)	Canada	Alberta	Community and registry	Case-control	-	4.96; 2.78-7.22	46.9	-	Alcohol-exposed (confirmed- unquantifiable)	typically- developing (No PAE) = NR	-
Mattson et al. (2010) - alcohol exposed analysis#	U.S & Finland	San Diego & Helsinki	Multi-site	Case-control	-	13.3; 7-21	57.14	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Unexposed controls (No PAE) = NR	-
Mattson et al. (2013) - alcohol exposed analysis <sup>†</sup>	U.S. & South Africa	CIFASD	Multi-site	Nested case- control	-	12.25; 8-17	52.5	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Unexposed controls (No PAE) = NR	-

McGee, Fryer, et al. (2008a)	U.S. & Canada	-	Online recruitment	Case-control	-	15.3; 13-18	48.7	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	Matched for age & sex
McGee, Schonfeld, et al. (2008b)	U.S	San Diego	FASD clinic	Nested case- control	-	11.28; 8.08- 15.8	43.3-48.9	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-
McGee et al. (2009)	U.S	San Diego	FASD clinic	Nested case- control	-	4.41; 3-5	56.8	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	Matched for age, sex, race/ethnicity & socioeconomic status
Migliorini et al. (2015)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	15; 12-17	60.4	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Controls (No PAE) = NR	-
Moore et al. (2021) - Atlanta cohort <sup>††</sup>	U.S	CIFASD I-III	FASD clinic	Case-control	-	NR; 5-16.9	53-62	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	Matched for age, ethnicity, socioeconomic status & geographic region
Moore et al. (2021) - San Diego cohort <sup>††</sup>	U.S	CIFASD I-III	FASD clinic	Case-control	-	NR; 5-16.9	69	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	As above
Muggli et al. (2017)	Australia	AQUA	Hospitals	Prospective cohort	-	Birth; NR	53	-	Any alcohol (Any PAE) = NR	Abstinent (No PAE) = NR	-
Nakhid et al. (2022)	Canada	Alberta	Diagnostic clinic	Case-control	-	11.05; 7.5-15	54.7	-	PAE (confirmed-unquantifiable) = NR	Unexposed controls (No PAE) = NR	-
Nguyen et al. (2014)	U.S	CIFASD	Multi-site	Nested case- control	-	12.3; 8-16	44-55	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	Age-corrected scores
Noland et al. (2003)	U.S.	-	Hospital	Nested case- control	-	Birth; NR & 4; NR	NR	-	Exposed (confirmed-unquantifiable) = NR	Non-exposed (No PAE) = NR	Physical Size: Adjusted for gestational age. See regression summary table. Sample included Cocaine exposure
O'Leary and Bower (2012)	Australia	WA data linkage	Admin data	Retrospectiv e cohort	41% Aboriginal Australian	NR; NR	NR	-	ICD alcohol-related diagnosis (confirmed-unquantifiable) = NR	No AUD	Adjusted for term births, Aboriginal status (outcome here non-Aboriginal only), appropriate fetal growth, ilicit drug use. Other potential confounders examined & not found to be influence results: marital status, parity, SES, pregnancy complications, smoking.
O'Leary et al. (2020)	Australia	WA data linkage	Admin data	Retrospectiv e cohort	Non-Indigenous Western Australians	NR; NR	NR	-	ICD alcohol-related diagnosis (confirmed-unquantifiable) = NR	No AUD	Matched for maternal age within the Indigenous status & the year of the child's birth at a ratio of 1:3 for non- Indigenous & 1:2 for Indigenous mothers.
Okah et al. (2005)	U.S	Kansas City	Admin data	Retrospectiv e cohort	-	Birth; NR	NR	-	Alcohol - yes (Any PAE) = NR	Alcohol - No (No PAE) = NR	Adjusted for maternal age, race, maternal education, marital status, interpregnancy interval, medical risk for LBW, Medicaid, prenatal care; sample without tobacco & illicit drug use
Panczakiewicz et al. (2016)	U.S	CIFASD III	Multi-site	Nested case- control	-	12.1; 5-16	NR	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-
Pfinder and Lhachimi (2020)	Germany	KIGGS	Multi-site	Nested case- control	-	14.4; 11-17	50.8	-	Low-moderate PAE (confirmed- unquantifiable) = NR	No (No PAE) = NR	Adjusted for adjustment for gender, age, birth weight, maternal age at birth of the child, ethnicity, socioeconomic status, exposure to smoke, smoking during pregnancy, at home & victim of sexual harassment.
Poth et al. (2023)	U.S	CIFASD-IV - San Diego	FASD Clinic	Nested case- control	Majority Caucasian	14.55; 12-17.11	50	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Controls (No PAE) = NR	-
Roos et al. (2021)	South Africa	DCHS	Antenatal clinics	Nested case- control	-	NR; 0.04-0.08	57-60	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Controls (No PAE) = NR	•
Schonfeld et al. (2005)	U.S	San Diego	FASD clinic	Nested case- control	-	13.5; 10-18.4	46.4	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Matched Control (No PAE) = NR	Matched for age, sex, handedness, socioeconomic status & ethnicity
Subramoney et al. (2022)	South Africa	DCHS	Antenatal clinic	Nested case- control	Low SES	2.81; 2-3	58.4	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-

Tamura et al. (2018)	Japan	Hokkaido	Hospitals & clinics	Prospective cohort	-	Birth; NR	NR	-	Current drinker (Any PAE) = NR	Never (no PAE) = NR	Maternal education level
Treit et al. (2020) - PAE analysis <sup>‡‡</sup>	Canada	NeuroDevNe t	FASD clinics	Nested case- control	-	12.5; 5-44	49.5	Chudley et al. (2005) & 4-Digit Code	Alcohol-exposed (confirmed- unquantifiable) = NR	Control (No PAE) = NR	-
Vaurio et al. (2011)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	10.53; 6-16	50	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-
Ware et al. (2012)	U.S	CIFASD	Multi-site	Case-control	-	12.10; 8-18	53.8	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-
Ware et al. (2013)	U.S	CIFASD II	Multi-site	Case-control	-	12.28; 8-16	55.9	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	-
Whaley et al. (2001)	U.S	UCLA	FASD clinic	Case-control	-	NR; 1.6-11.0	71.2	-	Alcohol-exposed (confirmed- unquantifiable) = NR	Non-exposed (No PAE) = NR	Matched for sex, age, IQ, outpatient or inpatient status
Yoshida et al. (2018)	Japan	Hofu database	Child health check data	Retrospectiv e cohort	-	3; NR	51		PAE - yes or sometimes (Any PAE) = NR	No PAE (No PAE) = 0g/w	Adjusted for child's sex, birth order, birth weight, history of otits media, mother's age at pregnancy, familial history of hearing impairment & prenatal smoking history.
Diagnosed Studies		•				•	•				
Adnams et al. (2001)	South Africa	-	School	Case-control	South African Coloured	6.9; 6.3-8	58.8	NR	FAS	Matched controls	Matched for age, sex, first language, family income & where possible school
Agnihotri et al. (2019)	Canada		Hospital	Case-control	-	13.5; 9.18- 17.95	53-56%	Chudley et al. (2005)	FASD	Non-exposed controls	Memory outcome: Adjusted for SES
Aragón, Coriale, et al. (2008a)	Italy	-	School	Case-control	-	6.13; 6-7	47.8-64.9	Hoyme et al. (2005)	FAS/pFAS	Matched controls	Matched for school grade & class
Aragón, Kalberg, et al. (2008b)	U.S.	-	Community- based	Case-control	Native American	11.5; 7-17	62.5-43.8	Hoyme et al. (2005)	FAS; pFAS	Matched controls	Matched for age, ethnicity, & community
Astley, Aylward, et al. (2009a)	U.S	UW FAS DPN	FASD clinic	Nested case- control	-	12.4; 8-15	50-66.7%	4 Digit Code	FAS/pFAS; SE-AE; ND-AE	Matched non- exposed controls	Matched for age, sex & race
Astley, Olson, et al. (2009b)	U.S.	UW FAS DPN	FASD clinic	Nested case- control	-	12.4; 8-15.9	67	4 Digit Code	FAS/pFAS; SE-AE; ND-AE	Matched non- exposed controls	Matched for age, sex & race
Bagheri et al. (1998)	U.S.	North Dakota FAS Registry	FASD clinic	Case-control	-	Birth; NR	NR	Sokol & Clarren 1989	FAS	Matched controls	Matched for age, county & sex
Barrett et al. (2019)	U.S.	CIFASD - Atlanta	FASD clinic	Nested case- control		10.9; 6-18	42.1-46.2	-	PAE (> 13 drinks/w or >4 drinks /occasion or FAS/pFAS	Typically- developing non- exposed controls	
Ben-Shachar et al. (2020)	South Africa	Cape Town LCS	Antenatal & follow-up diagnostic clinic	Nested case- control	Cape Coloured	16.3; NR	50-66.7	Hoyme et al. (2005)	FAS; pFAS; Non-syndromal	Typically developing non- exposed controls	-
Bernes et al. (2021)	U.S.	CIFASD II	FASD clinics	Nested case- control	-	11.8; 8-16	59.6-78	Jones et al 2006	>14 drinks/w or >4 drinks/occasion; FAS	Matched non- exposed or minimally exposed (<1 drink per w <2 drinks/occasion)	Matched for age, race/ethnicity, sex & socioeconomic status
Biffen et al. (2017)	South Africa	Cape Town LCS	Antenatal & follow-up diagnostic clinic	Nested case- control	Cape Coloured	10.6; 9-11	44-63	Hoyme et al. (2005)	FAS; pFAS; Non-syndromal	Typically developing non- exposed controls	See regression summary table

Blanck-Lubarsch, Dirksen, Feldmann, Sauerland and Hohoff (2019a)	Germany	-	Hospital	Case-control	Caucasian	8.4; 5.8-11.9	55	German guideline	FAS	Controls	-
Blanck-Lubarsch, Dirksen, Feldmann, Sauerland, Kirschneck, et al. (2019b)	Germany	-	Hospital	Case-control	Caucasian	8.4; 5.7-11.9	54.4	German guideline	FAS	Controls	-
Breiner et al. (2013)	Canada	Motherisk	Diagnostic clinic	Case-control	-	NR; 4.0-6.0	NR	Chudley et al. (2005)	FASD	Controls	-
Candelaria-Cook et al. (2021)	U.S.	New Mexico	FASD clinic	Case-control	-	10.6; 8.0-13.0	41%	NR	FAS/pFAS, ARND	Matched controls	Matched for age & gender
Chambers et al. (2019)	U.S.	CoFASP: Southwest	School	Case-control	-	Birth; NR & 7.12; NR	52	Hoyme et al. (2016)	≥ 3 drinks per occasion on at least 2 occasions or ≥ 6 per w for at leat 2 ws; FAS, pFAS, ARND	No FASD; M = 1.9 drinks usual drinking day first trimester; random sample matched control	Matched for school grade
Cheng et al. (2017)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.6; NR	44.6	Hoyme et al. (2005)	FAS/pFAS; Non-syndromal	Healthy controls	-
Colby et al. (2012)	U.S.	-	Multi-site	Case-control	-	Birth; NR & ~10; NR	52.2	4-Digit Code	≥14 drinks/w or ≥4 drinks/occasion (~M = 168g+/w); FAS, pFAS, ARND	Typically developing non- exposed controls	Sample included Methamphetamine exposure
Coles et al. (1997)	U.S.	Atlanta	Hospital	Nested case- control	Low socioeconomic statusAfrican American	Birth; NR & 7.6; NR	38.7-81.5	NR	Dysmorphic (including FAS) M=12.5 AA 02/w vs non-dysmorphic M=6.67 AA 02/w	Non-exposed controls	-
Coles et al. (2002)	U.S.	Atlanta	Hospital	Nested case- control	Low socioeconomic status, African American	15.08; NR	39-61	Dysmorphol ogy checklist	Dysmorphic (M=11.49 AA oz/w) vs non-dysmorphic (M=8.59 AA oz/w)	Non-exposed controls	-
Coles et al. (2010)	U.S.	Atlanta	Hospital	Nested case- control	Predominantly African American	22.8; NR	33.8-53.7	Dysmorphol ogy checklist	Dysmorphic (M = 13.59 AA oz/wl) vs non-dysmorphic (M= 8.03 AA oz/w)	Non-exposed controls	-
Coles et al. (2011)	U.S.	Atlanta	Hospital	Nested case- control	Predominantly African American, low SES	22.9; NR	27.8-46.7	Dysmorphol ogy checklist	Dysmorphic (M = 13.5 AA oz/wl) vs non-dysmorphic (M= 7.7 AA oz/w)	Non-exposed controls	-
Crawford et al. (2020)	New Zealand	-	Diagnostic clinic	Case-control	-	9.58; 8.0-12.0	60-77	Chudley et al. (2005)	FASD	Matched non- exposed controls	
Crocker et al. (2011)	U.S	San Diego	FASD clinic	Nested case- control	-	10.7; 7-14	50	Hoyme et al. (2005)	FASD (59% FAS)	Non-exposed (No PAE) = NR	Matched for age, sex, & race/ethnicity
Davies et al. (2017)	South Africa	Northern Cape	Hospital & follow-up at clinic	Nested case- control	Low SES	Birth; NR & ~1; NR & NR; 5-6	41.3	Hoyme et al. (2005)	FAS/pFAS, Alcohol-exposed (ie ARND)	Non-exposed controls	
De Guio et al. (2014)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	9; NR	33.3-53.3	Hoyme et al. (2005)	FAS (M=1.8 AA/day), alcohol exposed (AA/day = 0.5)	Non-exposed controls/minima Ily exposed	Matched for age. See regression summary table.

de Water et al. (2021)	U.S.	CIFASD - Minnesota	FASD clinic	Nested case- control	-	11.6; 8- 16	51.2	IOM (year NR)	> 13 drinks/ w or > 4 drinks per occasion at least once; FAS, pFAS, ARND	Non- exposed/minima Ily exposed (<1 drink/w, never > 2 drinks/occasion)	-
Dodge et al. (2020)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.4; 8-12	33.3-47.4	Hoyme et al. (2005)	FAS/pFAS (M= 2.8 oz AA/day) alcohol exposed (M=2.1 oz AA/day)	Non-exposed controls/minima lly exposed	Matched for age, sex, & intracranial volume
Doney et al. (2016)	Australia	Liliwan	Community- based	Case-control	Aboriginal Australian	8.7; 7.5-9.6	52.8	Chudley et al. (2005)	FASD	Non-exposed controls	-
Doney, Lucas, Jirikowic, et al. (2017a)	Australia	Liliwan	Community- based	Case-control	Aboriginal Australian	8.7; 7.5-9.6	52.8	Chudley et al. (2005)	FASD	Non-exposed controls	-
Doney, Lucas, Watkins, et al. (2017b)	Australia	Liliwan	Community- based	Case-control	Aboriginal Australian	8.7; 7.5-9.6	52.8	Chudley et al. (2005)	FASD	Non-exposed controls	-
Dudek et al. (2014)	Canada	Motherisk	Diagnostic clinic	Case-control	-	12.6; 11.1-14.8	61.1-62.4	Chudley et al. (2005)	ARND	Typically developing matched controls	Matched for age & sex. Structural neuro outcomes: Adjusted for intracranial volume
Fagerlund et al. (2011)	Finland	-	Hospital	Case-control	-	13.5; 8-21	39.7	Hoyme et al. (2005)	FASD	Typically developing matched controls	Matched for age, sex & geographical region
Fagerlund et al. (2012)	Finland	-	Hospital	Case-control	-	13.1; NR	39.7-45	Hoyme et al. (2005)	FASD	Typically developing matched controls	Matched for age, sex & geographical region
Fan et al. (2016)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	9.4; NR	50-53	Hoyme et al. (2005)	FAS/pFAS (M oz AA/day = 1.3) alcohol exposed (M oz AA/day = 0.5)	Non-exposed controls	See regression summary table
Foroud et al. (2012)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	4.8; NR & 8.8; NR	46.9-60.0	Hoyme et al. (2005)	FAS/pFAS (M oz AA/day = 1.5) alcohol exposed (M oz AA/day = 1.3)	Non-exposed controls	-
Fryer et al. (2009)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	13.5; 8-18	57	Hoyme et al. (2005)	FASD (60% FAS)	Non-exposed (No PAE) = NR	Matched for age, sex, & socioeconomic status
Fryer et al. (2012)	U.S	San Diego	FASD clinic	Nested case- control	Majority Caucasian	13.13; 9-21	57.1	Hoyme et al. (2005)	FASD (57% FAS)	Non-exposed (No PAE) = NR	-
Gautam et al. (2014)	U.S.	CIFASD-LA	FASD clinic	Nested case- control	-	11.5; 6.2-17.6	NR	Hoyme et al. (2005)	FASD (> 13 drinks/w or > 4 drinks/occasion)	Matched controls	Matched for age
Gomez et al. (2020)	South Africa	FASER database	School	Nested case- control	Cape Coloured	6.93; 5-9	50.1-50.3	Hoyme et al 2016	FAS, pFAS, ARND, all FASD	Controls with normal growth	Matched for age
Greenbaum et al. (2009)	Canada	Motherisk	Diagnostic clinic	Case-control	-	9; 6-13	50.5	Chudley et al. (2005)	FASD	Typically developing controls	Adjusted for socioeconomic status, tobacco use, abuse, & foster/adoption history
Hansen and Jirikowic (2013)	U.S	UW FAS DPN	FASD clinic	Nested case- control		8.5; 5-11	56.5	4-Digit Code	FASD	Typically developing controls	
Hasken et al. (2021)	South Africa	CIFASD	School	Case-control	71% mixed race ancestry "Cape Coloured"	7; NR	~50	Hoyme et al 2016	FAS, pFAS, ARND	Unexposed controls	-

Howell et al. (2006)	U.S	Atlanta	Hospital	Nested case- control	Predominantly African American, Iow SES	15.1; NR	43.6	Dysmorphol ogy checklist	Dysmorphic (M = 12.17 AA oz/wl) vs non-dysmorphic (M= 10.69 AA oz/w)	Unexposed controls	-
Inkelis et al. (2020)	U.S	Seattle (FAS Follow-up)	Antenatal & follow-up clinic	Nested case- control	-	19; 13-30	59	Steissguth et al 1991	FASD	Healthy controls	Matched for age & ethnicity
Jacobson et al. (2011)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	NR; 8-12	36.5	Hoyme et al. (2005)	FAS (M oz AA/day = 2.2) alcohol exposed (M oz AA/day = 2.4)	Unexposed/ minimally exposed controls M = 0.002 oz AA/day	-
Jirikowic, Olson, et al. (2008a)	U.S	UW FAS DPN	FASD clinic	Nested case- control	-	6.7; 5-8	54.9	4-Digit Code	FASD	Typically developing controls	-
Jirikowic, Kartin, et al. (2008b)	U.S	UW FAS DPN	FASD clinic	Nested case- control	-	6.5; 5-8.6	52.1	4-Digit Code	FASD	Typically developing controls	
Joseph et al. (2014)	South Africa	Cape Town LCS	NR	Case-control	Cape Coloured	11.6; NR	47.6	NR	FAS/pFAS (M oz AA/day = 2.8)	Controls	-
Kable et al. (2021)	Ukraine	CIFASD	Prenatal appointments & clinic follow- up	Nested case- control	-	NR; 3.5-4.5	40-57.9	Hoyme et al. (2016)	FAS/pFAS (M=0.38 AA per day at conception), ARND (M=0.62 AA per day at conception)	Non-exposed control	
Kaemingk and Halverson (2000)	U.S	-	School	Case-control	Native American	NR; 6-16	60	NR	FAS/FAE (FASD)	Matched controls	Matched for age & sex
Kaemingk et al. (2003)	U.S	-	School	Case-control	Native American	11.1; 6-16	60	NR	FAS/FAE (FASD)	Matched controls	Matched for age & sex
Kalberg et al. (2013)	South Africa	-	School	Nested case- control	-	6.95; NR	45.1	Hoyme et al. (2005)	FASD	Matched controls	Matched for age & sex
Kerns et al. (2016)	Canada	-	Community- based	Case-control	-	11.2; 8-14	54.5	4-Digit Code & Chudley et al. (2005)	FASD	Matched controls	Matched for age & sex
Kodituwakku et al. (2001)	U.S	-	Register & community	Case-control	-	11.12; 7.67- 19.42	65	RSA	Alcohol exposed (FAS and non- dysmorphic)	Matched controls	Matched for age, gender & ethnic background
Kodituwakku et al. (2006a)	South Africa		School	Nested case- control	Cape Coloured	NR; 7.59; 6-9	47.1	Hoyme et al. (2005)	FAS	Matched controls	Matched for age, sex, family income, & school grade
Kodituwakku et al. (2006b)	Italy	-	School	Case-control	-	6.75; 6.1-7.7	~49	Hoyme et al. (2005)	FAS, pFAS, ARND	Matched controls	Matched for school grade
Kooistra et al. (2009)	Canada	-	FASD clinic	Case-control	-	8.95; 7-10	53.6	4-Digit Code	FASD	Controls	-
Krueger et al. (2020)	U.S	CIFASD- Minnesota	FASD clinic	Nested case- control	-	11.87; 8-16	50.78	Hoyme et al. (2016)	FASD	Unexposed controls	-
Lane et al. (2014)	Canada	-	FASD clinic	Case-control	-	11.73; 7-12	35.7	Chudley et al. (2005)	FASD	Typically developing non- exposed controls	Matched for gender & mental age
Lewis et al. (2015)* - Cape Town cohort <sup>§</sup>	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.3; 8.7-12.2 & 14.4; 13.3- 16.5	51.0 & 57.4	Chudley et al. (2005)	FAS/pFAS and alcohol exposed.	Unexposed controls	See regression summary table
Li et al. (2009)	U.S	Atlanta	Hospital	Nested case- control	Predominantly African American, Iow SES	22.9; 19-27	20.7-48	Dysmorphol ogy checklist	Dysmorphic (M = 14.7 AA oz/w) vs non-dysmorphic (M= 8.7 AA oz/w)	Unexposed controls	-

Lidstone et al. (2020)	U.S	-	FASD clinic	Case-control	-	12.15; 7-17	31-60	NR	FASD	Typically developing controls	-
Lindinger et al. (2016)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.9; 9-11	37.5-58.8	Hoyme et al. (2005)	FAS (M AA oz/day = 1.8), pFAS (m AA oz/day = 1) & exposed (M AA oz/day = 0.5)	Unexposed controls	-
Little and Beaulieu (2020)	Canada	Neuro- DevNet	FASD clinics	Case-control	-	12.3; 5.7-18.9	41.8	Chudley et al. (2005)	FASD	Typically developing controls	-
Lucas, Doney, et al. (2016a)	Australia	Liliwan	Community- based	Case-control	Aboriginal Australian	8.7; 7.5-9.6	52.8	Chudley et al. (2005)	FASD	No FASD	-
Lucas, Latimer, Doney, et al. (2016b)	Australia	Liliwan	Community- based	Case-control	Aboriginal Australian	8.7; 7.5-9.6	53	Chudley et al. (2005)	FASD	No FASD	•
Lucas, Latimer, Fitzpatrick, et al. (2016c)	Australia	Liliwan	Community- based	Case-control	Aboriginal Australian	8; 7-9	53	Chudley et al. (2005)	FASD	No FASD	
Lynch et al. (2015)	U.S	Atlanta	Hospital	Nested case- control	Predominantly African American, Iow SES	Birth; NR & ~22; NR	39 - 47.9	Dysmorphol ogy checklist	Dysmorphic (M=13.13 AA oz/w); Exposed cognitive affected (M=8.09 AA oz/w); exposed not cognitively affected (M=7.95 AA oz/w)	Unexposed controls	-
Lynch et al. (2017)	U.S	Atlanta	Hospital	Nested case- control	Predominantly African American, Iow SES	22; NR	39 - 47.9	Dysmorphol ogy checklist	Exposed, dysmorphic (pFAS); Exposed, cognitively effected (ARND/Others)	Unexposed controls	-
Malisza et al. (2012)	Canada	CADEC	FASD clinic	Case-control	-	12.4; 10-14	63.6 - 76.2	Chudley et al. (2005)	ARND	Typically developing controls	Matched for age & gender
Mattson et al. (1997)	U.S	San Diego	FASD clinic	Case-control	Majority Caucasian	8.5; NR	50	NR	FAS, PEA	Matched controls	Matched for age & sex
Mattson and Riley (2000)	U.S	San Diego	FASD clinic	Case-control	Majority Caucasian	8.8; 4 - 16	48.4	NR	FASD (FAS & PEA)	Matched controls	Matched for age, sex, socioeconomic status & ethnicity
Mattson and Riley (1999)	U.S	San Diego	FASD clinic	Case-control	Majority Caucasian	12.1; 8.5 - 18	47.3	NR	FASD (FAS, PEA)	Matched controls	Matched for age, sex, ethnicity
Mattson and Roebuck (2002)	U.S	San Diego	FASD clinic	Case-control	Majority Caucasian	12.1; 8.5 - 18	45.7	NR	FASD (FAS & PEA)	Matched controls	Matched for age, sex, socioeconomic status & ethnicity
Mattson et al. (2010) - FAS analysis#	U.S & Finland	San Diego & Helsinki	Multi-site	Case-control	-	13.5; 7-21	40	NR	FAS	Non-exposed typically developing	
Mattson et al. (2013) - FAS analysis <sup>†</sup>	U.S. & South Africa	CIFASD	Multi-site	Nested case- control	-	12.25; 8-17	48.6-75.7	CIFASD	FAS, AE without FAS	Unexposed controls	•
Mattson et al. (2023)	U.S	CIFASD	Multi-site	Nested case- control	-	10.87; 4-17	57.2	CIFASD	Majority FASD	Unexposed controls	-
May et al. (2000)	South Africa	Western Cape	School	Case-control	Majority Coloured/black	6.6; NR	52.8	Stratton et al 1996	FAS	Matched controls	Matched for age, sex & classroom
May et al. (2006)	Italy	-	School	Case-control	-	6.7; NR	51	Hoyme et al. (2005)	FAS, pFAS, ARND	Non-FASD randomly selected controls	Matched for school grade
May et al. (2007)	South Africa	Western Cape	School	Case-control	Majority Coloured/black	7.3; NR	47.6-61.1	Hoyme et al. (2005)	FAS (M=13 drinks/w), pFAS (M=4.9 drinks/w)	Random sample matched control	Matched for school grade

May et al. (2010) - Italian Cohort <sup>‡</sup>	Italy	-	School	Case-control	-	6.6; NR	NR	Hoyme et al. (2005)	FASD	Randomly selected typical controls	Matched for age, sex, & community residence
May et al. (2010) - South African cohort <sup>‡</sup>	South Africa	-	School	Case-control	-	7.5; NR	NR	Hoyme et al. (2005)	FASD	Randomly selected typical controls	Matched for age, sex, & community residence
May et al. (2013a)	South Africa	-	School	Case-control	-	6.8; NR	49	Hoyme et al. (2005)	FAS, pFAS, ARND	Randomly selected typical controls	Matched for school grade
May et al. (2014)	U.S	Midwestern	School	Case-control	Majority caucasian	6.9; 6-7; NR	50.1	Hoyme et al. (2005)	FAS, pFAS, ARND	Randomly selected typical controls	Matched for school grade
May et al. (2015)	U.S.	Rocky Mountain	School	Case-control	Predominantly middle class	7; NR; NR	54.5	Hoyme et al. (2005)	M=5.3 drinks on a typical drinking day; FAS, pFAS	Random sample matched controls	Matched for school grade
May et al. (2016)	South Africa	-	School	Case-control	-	6.6; 6-7	52.9	Hoyme et al. (2005)	FAS (16.5 drinks/w), pFAS (4.5 drinks/w), ARND (8.4 drinks/w)	Random sample matched control	Matched for school grade
May et al. (2017b)	South Africa		School	Case-control	-	7.85; NR	53.6	Hoyme et al. (2005)	FAS, pFAS, ARND	Unexposed randomly selected typical controls	Matched for school grade. See regression summary table
May, Hasken, Bozeman, et al. (2020a)	U.S.	CoFASP: Southeast	School	Case-control	-	Birth; NR & ~6.7; NR	~55	Hoyme et al. (2016)	M=3.4 drinks/day on typical drinking day 1st trimester; FAS, pFAS, ARND; Exposure level NR	Random sample matched controls	Matched for school grade
May, Hasken, Stegall, et al. (2020b)	U.S.	CoFASP: Midwestern	School	Case-control	Primarily white non-Hispanic (85%)	~6.8; NR	36.4 - 60.9	Hoyme et al. (2016)	M = 3.2 drinks/day on usual drinking day 1st trimester; FAS, pFAS, ARND	Random sample matched controls	Matched for school grade
May, Hasken, Baete, et al. (2020c)	U.S.	CoFASP: Rocky Mountain	School	Case-control	-	Birth; NR & ~6.9; NR	50-75	Hoyme et al. (2016)	M=4.1 drinks on a typical drinking day 1st trimester; FAS, pFAS, ARND	Random sample matched controls	Matched for school grade
May et al. (2021)	U.S	CoFASP: South Eastern	School	Case-control	Majority Caucasian	6.9; 6-7	50	Hoyme et al. (2016)	FASD	Randomly selected typical controls	Matched for school grade
McLachlan et al. (2019)	Canada	Kids Brain Health Network (NeuroDevN et)	NR	Case-control	-	13.5; 7-18	21 - 40	Chudley et al. (2005)	PAE (FAS, pFAS, ARND)	Typically developing controls	-
McLachlan et al. (2020)	Canada	Canadian National FASD Database	FASD Clinics	Nested case- control	-	12.7; 7 - 18.5	40 - 50.7	Chudley et al. (2005)	PAE, FAS/pFAS. ARND	Matched typical controls	Matched for age & sex
Meintjes et al. (2014)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.4; 9-11	50.9	Hoyme et al. (2005)	FAS (M oz AA/day =1.9); pFAS (M oz AA/day =1); HE (M oz AA/day = 0.5	Unexposed/mini mally exposed controls M = 0.01 oz AA/day	
Miles et al. (2021)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	11.2; 9-14	50	Hoyme et al. (2005)	FAS/pFASD ( M oz AA/day = 2.1); HE (M oz AA/day = 1.6)	Unexposed/mini mally exposed controls M = 0.002 oz AA/day	
Moore et al. (2002)	U.S		Multi-site	Case-control	-	NR; 1 - >40yrs	50.9 - 68.3	Stratton et al 1996	FAS, pFAS	Controls	Adjusted for age & sex

Naidoo et al. (2005)	South Africa	-	School	Case-control	-	~9; NR	NR	NR	FAS	Matched controls	Matched for age, gender & social class
Nardelli et al. (2011)	Canada	-	FASD clinic	Case-control	-	11.3; 6-17	57.1	4-Digit Code	FASD	Matched controls	Matched for age & sex
Nayak et al. (2012)	India	-	Community- based	Case-control	-	6.1; NR	45.3	4-Digit Code	FASD	Matched controls	Matched for age & sex
O'Conaill et al. (2015)	Canada	Manitoba	FASD clinic	Case-control	-	12.24; 10-14	63.6-89.5	Chudley et al. (2005)	ARND	Matched controls	Matched for age, sex, IQ, SES
O'Hare et al. (2009)	U.S	UCLA	FASD clinic	Nested case- control	-	10.8; 7-15	50	4-Digit Code	FASD	Typically developing non- exposed controls	-
Olswang et al. (2010)	U.S	-	School	Case-control	-	9.1; 7.5-11.8	50	4-Digit Code	FASD	Matched controls	Matched for sex, age, teacher-rated cognitive abilities, & classroom
Paolozza, Rasmussen, et al. (2014a)	Canada	NeuroDevNe t	FASD clinics	Case-control	-	11.2; 5-17	48.6	Chudley et al. (2005)	FASD	Typically developing controls	
Paolozza, Treit, et al. (2014b)	Canada	NeuroDevNe t	FASD clinics	Nested case- control	-	12.4; 7-18	39-53	Chudley et al. (2005)	FASD	Typically developing controls	-
Paolozza, Rasmussen, et al. (2014c)	Canada	NeuroDevNe t	FASD clinics	Case-control	-	10.8; 5-17	50	Chudley et al. (2005)	FASD	Matched typical controls	Matched for geographic area, age & sex
Pei et al. (2011)	Canada	-	FASD clinic	Case-control	-	8.53; 6 - 12	48.5	Chudley et al. (2005)	FASD	Matched typical controls	Matched for sex & age
Pinner et al. (2020)	U.S	New Mexico Cetnre for Developmen tal Disability	NR	Nested case- control	-	16.3; 12-21	66.6	Stratton et al 1996	FASD	Healthy controls	-
Popova et al. (2019)	Canada	wно	School	Case-control	-	~8.5; NR	~55	Chudley et al. (2005)	FAS, pFAS, ARND	Random sample	-
Quattlebaum and O'Connor (2013)	U.S	UCLA	NR	Case-control	-	8.53; 6-12	52.8	4-Digit Code	Alcohol exposed (FAS, pFASD, ARND)	Non-exposed controls	-
Rajaprakash et al. (2014)	Canada	Motherisk	FASD clinic	Case-control	-	11.2; 8.1-15.6	52	Chudley et al. (2005)	ARND	Typically developing non- exposed controls	-
Rasmussen et al. (2009)	Canada	-	FASD clinic	Case-control	-	6.35; 4-8	52.8	4-Digit Code	FASD	Typically developing controls	-
Rasmussen, Becker, et al. (2011a)	Canada	-	Respite program	Nested case- control	Majority First Nations Canadian	5.4; 3-8	56.6	4-Digit Code	ALC exposed (60% diagnosis of FASD)	Non-exposed controls	-
Rasmussen, Soleimani, et al. (2011b)	Canada		FASD clinic	Case-control	-	9.43; 6-17	56	4-Digit Code	PAE/FASD	Typically developing controls	-
Rasmussen et al. (2013)	Canada	-	FASD clinic	Case-control	-	11.44; 6-16	33.4-43.8	4-Digit Code	FASD	Typically developing controls	-
Riley et al. (1995)	U.S	-	NR	Case-control	-	13; 8-18	68	NR	FAS & PAE	Matched typical controls	Matched for age & sex

Robertson et al. (2016)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.7; NR	55.9	Hoyme et al. (2005)	FAS/pFAS (M oz AA/day 1.3); HE nonsyndromal (M oz AA/day = 0.5)	Unexposed controls	See regression summary table
Rockhold et al. (2021)	U.S	CIFASD-4- Minnesota	FASD clinic	Nested case- control	Majority Caucasian	11.85; NR	49.5	4-Digit Code	PAE (included FAS, pFAS & ARND)	Controls	-
Roediger et al. (2021)	U.S	CIFASD (2017-2019) - Minnesota	FASD clinic	Nested case- control	Majority Caucasian	12.1; 8-16	49.36	Hoyme et al. (2016)	PAE included FAS, pFAS & ARND)	Controls	-
Roussotte et al. (2012)*	U.S & South Africa	CIFASD	Multi-site	Nested case- control	South Africa - Cape Coloured	12.47; NR	52.9	Hoyme et al. (2005)	FASD	Control	See regression summary table
Schonfeld et al. (2001)	U.S	San Diego	FASD clinic	Case-control	Majority Caucasian	11.6; 8-15	46	NR	FAS & PEA	Unexposed controls	Matched for age
Sowell et al. (2001)	U.S	San Diego	FASD clinic	Case-control	-	13; 8-25	46.3	NR	ALC (FAS & PEA)	Unexposed controls	-
Sowell et al. (2008)	U.S	UCLA	FASD clinic	Case-control	-	10.8; 7-15	47.2	4-Digit Code	FASD	Unexposed typically developing controls	-
Spottiswoode et al. (2011)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	9.7-13.7	23-1 - 41.7	Hoyme et al. (2005)	ALC (included FAS and pFAS) M oz AA/day = 2.7	Matched unexposed/mini mally exposed control (M oz AA/day = 0.004)	-
Stevens et al. (2012)	Canada	Motherisk	FASD clinic	Case-control	-	12.5; 9-16	48.8	Chudley et al. (2005) & 4-Digit Code	FASD	Typically developing controls	-
Stevens et al. (2015)	Canada	Motherisk	FASD clinic	Case-control	-	10.27; 8-12	53.4	Chudley et al. (2005) & 4-Digit Code	FASD	Typically developing controls	
Stevens et al. (2017)	Canada	Motherisk	FASD clinic	Case-control	-	10.21; 8-12	53	Chudley et al. (2005) & 4-Digit Code	FASD	Typically developing controls	-
Stromland (1985)	Sweeden	Goteborg	Hospital	Case-control	All caucasion	NR; Birth - 16	NR	Rosett 1980	FAS	Matched controls	Matched for sex & age
Sullivan et al. (2020)	U.S	Seattle (FAS Follow-up)	Antenatal & follow-up clinic	Nested case- control	-	19.94; 13-37	49.4	1994 Criteria (author NR)	FAS, FAE	Matched controls	Matched for sex & age
Suttie et al. (2013)	South Africa	Cape Town LCS	Antenatal & follow-up clinic	Nested case- control	Cape Coloured	10.2; NR	50	Hoyme et al. (2005)	FAS (M oz AA/day = 1.8). pFAS (M oz AA/day = 1.2); HE (M oz AA/day 1.3)	Unexposed controls	Matched for age
Suttie et al. (2018)	U.S	CIFASD	FASD clinics	Case-control	-	12.6; NR	60.5	Hoyme et al. (2016)	FAS & HE	Controls	-
Taggart et al. (2017)	U.S.	San Diego	FASD clinic	Case-control	-	~11; 7-17	59	CIFASD	FASD	Non-exposed (No PAE) = NR	
Thorne (2017)	U.S	UW FAS DPN	FASD clinic	Case-control	-	9.68; 7-12	54.8	4-Digit Code	FASD	Typically developing controls	Matched for age
Treit et al. (2016)	Canada	-	FASD clinics	Case-control	-	12.2; 5-19	50.1	Chudley et al. (2005) & 4-Digit Code	PAE( FAS, pFAS, SE, NB/ARND)	Controls	-

Treit et al. (2017)	Canada	Alberta	FASD clinics	Case-control	-	13.7; 5-32	54.2	Chudley et al. (2005) & 4-Digit Code	FASD	Typically developing non- exposed controls	-
Treit et al. (2020) - FASD analysis <sup>‡‡</sup>	Canada	NeuroDevNe t	FASD clinics	Nested case- control	-	12.5; 5-44	49.5	Chudley et al. (2005) & 4-Digit Code	Dysmorphic FASD; Non-Dysmorphic FASD	Control (No PAE) = NR	-
Uecker and Nadel (1996)	U.S	-	School	Case-control	Native American	10.02; NR	73	Gestalt	FAS	Matched controls	Matched for age
Viljoen et al. (2005)	South Africa	Western Cape	School	Case-control	Predominantly Coloured/black	~6.5; NR	~46.5	IOM 1996	FAS, pFAS, ARND	Random matched controls	Matched for school grade
Walthall et al. (2008)	U.S	UCLA	FASD clinic	Case-control	-	8.5; 6-12	51	4-Digit Code	ALC (FAS, pFAS, SE)	Typically developing controls	See regression summary table
Ware et al. (2021)	Canada	KBHN (previously Neuro- DevNet)	FASD clinics	Case-control	-	13; 6-18	43.5	Chudley et al. (2005)	PAE (FAS/pFAS, ARND)	Typically developing controls	-
Way and Rojahn (2012)	U.S	-	Community- based	Case-control	-	8.8; 5.5-14.4	37.5	-	PAE (FAS, pFAS, ARND)	Typically developing matched controls	Matched for age & sex
Wheeler et al. (2012)	Canada	Motherisk	FASD clinic	Case-control	-	12.58; 10 - 14	57.5	Chudley et al. (2005) & 4-Digit Code	ARND	Typically developing controls	-
Willoughby et al. (2008)	Canada	Motherisk	FASD clinic	Case-control	-	Birth; NR	38.9 - 73.7	Chudley et al. (2005)	FASD (FAS or ARND)	Typically developing unexposed controls	-
Wozniak et al. (2006)	U.S.	Uni Minnesota	FASD clinic	Case-control	-	Birth; NR & ~12.2; 10-13	~48	Digit Code	FASD (pFAS, SE, ND)	Typically developing matched controls	Matched for age & gender
Wozniak et al. (2009)	U.S.	Uni Minnesota	FASD clinic	Case-control	-	~13; 10-17	~54	4-Digit Code	FASD (FAS, pFAS, SE)	Typically developing controls	-
Wozniak et al. (2013)	U.S	Uni Minnesota	FASD clinic	Case-control	-	14; 10-17	54.5	4-Digit Code & Hoyme et al. (2005)	FASD (FAS, pFAS, ARND)	Typically developing unexposed controls	-
Yang, Phillips, et al. (2012a)	U.S. & South Africa	CIFASD	Multi-site	Case-control	South Africa cohort - Cape Coloured	12.55; 8-16	46.4	Hoyme et al. (2005)	FASD	Typically developing unexposed controls	-
Yang, Roussotte, et al. (2012b)	U.S. & South Africa	CIFASD	Multi-site	Case-control	South Africa cohort - Cape Coloured	13.2; 8-16	55.9	Hoyme et al. (2005)	FASD	Typically developing unexposed controls	
Zhou et al. (2018)	Canada	Neuro- DevNet	FASD clinics	Nested case- control	-	12.45; 5.8-18.5	46.4	Chudley et al. (2005) & 4-Digit Code	PAE combined, FAS, pFAS & ARND	Typically developing controls	Matched for age & sex

Notes: \* indicates studies with regression data

#) Mattson et al 2010 has both an alcohol exposed analysis and diagnosed analysis.

†) Mattson et al 2013 has both an alcohol exposed analysis and diagnosed analysis.

††) Moore et al 2021 reports data from two separate cohorts.

‡‡) Treit et al 2020 has both an alcohol exposed analysis and diagnosed analysis.

§) Lewis et al 2015 reports data from two separate cohorts. Data from the Detroit cohort was not included due to light prenatal alcohol exposure in the control population.

\*) May et al 2010 reports data from three separate cohorts. Data from the Native American cohort was not included due to high prenatal alcohol exposure rates in the control population.

AE, alcohol exposed; ARND, alcohol related neurodevelopmental disorder; CIFASD, Collaborative Initiative on the Fetal Alcohol Spectrum Disorders; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; M oz AA/day, Mean ounces of absolute alcohol per day; ND, neurobehavioural disorder; PAE, prenatal alcohol exposure; pFAS, partial FAS; SE, static encephalopathy; w, week

