PREPARE

Informing Policy with Evidence

Measuring prevalence of foetal alcohol spectrum disorder in the UK: a scoping study

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Researchers at the University of York conducted the research, with contributions from topic and methodological experts, who engaged in a roundtable discussion. We are grateful for their expertise, and for useful advice on economic modelling from Professor Mark Sculpher (Centre for Health Economics, University of York) and Professor Alan Brennan (University of Sheffield).

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Key messages

- Drinking during pregnancy can affect the developing foetus, risking Foetal Alcohol Spectrum Disorder (FASD). This can result in physical, mental, and behavioural problems for children, including learning difficulties.
- FASD is a preventable condition which can have a significant impact on life chances, and societal costs.
- The UK has high rates of alcohol consumption, binge drinking and prenatal alcohol exposure.
- The scale of FASD and its impact on the population are believed to be under-recognised. There are currently no reliable estimates of the prevalence, incidence or cost impact of FASD in England.
- We reviewed published literature on reported FASD prevalence estimates and the relationship between quantity and patterns of alcohol drinking during pregnancy, and risks of FASD.
- Our review of international prevalence studies revealed a very wide range of estimates of national prevalence of FASD, notably affected by differences in study methodology.
    - Large sample studies based on passive surveillance or analysis of birth registries estimated prevalence of less than 1 per 1000 children.
    - Case ascertainment studies in school-aged children estimated much higher prevalence, although there was still a wide range (6 per 1000 to 80 per 1000).
- Given the very different methods used to measure exposure to alcohol, it was not appropriate to synthesise the prevalence estimates.
- Our review of dose-response and drinking patterns illustrates differing methods, drinking measures and FASD diagnosis thresholds, again making formal synthesis inappropriate.
- There is evidence that higher levels of drinking during pregnancy increases the risk of FASD, but the nature of the 'dose-response' relationship is unclear, and it is not possible to identify a threshold below which drinking can be viewed as 'safe'. This supports the position of the UK Chief Medical Officers, who recommend that for women who are pregnant or planning a pregnancy, the safest approach is not to drink alcohol at all.
    - Even if it were possible to identify a clear relationship, sharing estimates of 'dose response' could feasibly weaken the clear, understandable current message that any drinking during pregnancy is potentially harmful.
- We consulted academic and clinical experts in FASD in a roundtable discussion about measuring prevalence of FASD.
    - The expert group believed that a national prevalence study is desirable to inform future policy and practice.

    - The group favoured an *active school-based case ascertainment approach* supplemented by statistical correction reflecting likely under-reporting, along with consent for future data linkage and follow-up.
    - This would cost around £1000 per child included, plus costs of training staff to screen children and provide advice and services for those newly diagnosed.
- Such a study would unavoidably have limitations. An existing pilot study was unable to recruit any children from specialist schools providing social, emotional and mental health support, and even in mainstream schools there was a lack of consent in high-risk groups such as children under local authority care.
- Questioning women about drinking during pregnancy requires a detailed and sensitive approach, reducing stigma and encouraging transparency.
- We question whether a more precise prevalence estimate would be an efficient way to influence policy and practice, compared with a modelled prevalence estimate.
    - Would it strengthen the prevention message – particularly given that guidance from the UK Chief Medical Officers clearly recommends total abstinence?
    - Should it be necessary for children to have a diagnosis of FASD to access services?
- We recommend that a first step should be to commission a modelling study, estimating the likely range of prevalence from existing information (including the prevalence estimates in our review).
- This should be supplemented with a value of information (VoI) analysis to assess the value of more research to increase the precision of prevalence estimates, in terms of the likely impact of resulting changes in policy and practice and usefully informing decisions on future research in this area.

1. Background, aims and objectives

Since 2016, UK guidelines have recommended that women who are pregnant should not drink any alcohol, to minimise risks to their baby.[1] The guideline highlights the wide range of potentially lifelong impacts of alcohol on a developing foetus, known under the umbrella term of 'foetal alcohol spectrum disorders' (FASD). FASD can result in physical, mental, and behavioural problems, including learning difficulties, and individuals with FASD are reported to be more likely to need health care and educational support, and may disproportionately appear in the criminal justice system.[2] The severity and nature of FASD is associated with the amount drunk and when drinking occurs during the development of the foetus. Research on the effects of low levels of drinking in pregnancy can be difficult to interpret, and for this reason, national guidance takes the 'precautionary' approach of advocating total abstinence.[1] Drinking heavily during pregnancy can cause a baby to develop foetal alcohol syndrome (FAS), which results in restricted growth, facial abnormalities, learning and behavioural disorders.

The UK has high rates of alcohol consumption, binge drinking and prenatal alcohol exposure. In 2023, a report stated that UK women are the biggest binge drinkers in the OECD, with 26% of women drinking at least six drinks in a single session, at least once a month.[3] A 2015 study suggested that three-quarters of women in the UK consumed some alcohol during pregnancy, with a third reporting binge drinking at least once.[4] The scale of FASD and its impact on the population are believed to be 'grossly under-recognised.[5]

FASD is a preventable condition which can have a significant impact on life chances and societal costs. There are currently no reliable estimates of the prevalence, incidence or costs of FASD in England.

1.1. Research aims

The aims of this study are:

1. To synthesise and interpret existing prevalence studies, their methods and findings, summarising prevalence estimates in high-income countries like the UK.
2. To synthesise evidence on patterns of drinking and the 'dose-response' relationship between alcohol consumption during pregnancy and FASD.
3. To produce recommendations for future research on the prevalence of FASD.

1.2. Our approach

To address the study aims, our approach comprises:

1. A scoping review of existing prevalence studies, describing and critically appraising the methods and synthesising estimates of prevalence to produce a plausible range of prevalence within which the English population is likely to lie.
2. A scoping review of studies of the association between volume of alcohol during pregnancy ('dose-response'), stage of pregnancy (e.g. by trimester) and patterns of drinking during pregnancy (e.g. binge drinking) and the risks, levels and severity of FASD.
3. An online 'roundtable' event with multidisciplinary clinical and methodological experts to advise on possible study designs and methodology for a future prevalence study.
4. Reflecting on a range of options for future research, highlighting practical and ethical concerns and identifying strengths and weaknesses.

1.3. Ethics and governance

The University of York's Health Sciences Research Governance Committee conducted an ethical review of our plans. Our expert roundtable involved methodologists and clinicians, not patients, therefore NHS ethical review was not required.

2. Scoping reviews: measuring FASD prevalence and associations with levels and patterns of drinking during pregnancy

Our scoping review follows the principles of the PRISMA-ScR statement[6] to describe current prevalence estimates for FASD in countries similar to the UK and map the evidence on the dose-response relationship between alcohol drinking during pregnancy and a diagnosis of FASD.

2.1. Inclusion and exclusion criteria

We established strict inclusion and exclusion criteria (Table 1).

Table 1 Inclusion and exclusion criteria

	Inclusion	Exclusion
Prevalence		
Population	General population	Special populations such as people who have been convicted or children in foster care
Outcomes	Diagnosis of FASD or disaggregated as FAS, partial FAS and Alcohol Related Birth Defects (ARBD) where the diagnostic guideline or case definition used to ascertain cases is specified.	No prevalence data, reports on the prevalence of traits or conditions related to FASD (for example, the prevalence of externalising behavioural problems without reaching a diagnosis of FASD).
Study designs	Observational studies that provide prevalence and a measure of uncertainty or the necessary information to calculate uncertainty (such as sample size or the number of cases).	Case reports, case series, editorials, letters, and pre-print reports.
Dose-response		
Population	Pregnant women sampled from the general population	Pregnant women with drug addiction
Exposure	Patterns or levels of alcohol consumption during pregnancy, including (but not limited to) binge drinking, daily drinking, or occasional drinking	Patterns or levels of alcohol consumption before pregnancy
Outcomes	Offspring with FASD diagnosis or disaggregated as FAS, partial FAS, and/or ARBD	Measure of detrimental effects of alcohol exposure without a diagnosis of FASD. Studies only reporting cases of FAS
Study designs	Original research. Observational studies	Case reports, case series, editorials, letters, and pre-print reports.
Both reviews		
Setting	High-income countries comparable to the UK	Low- and middle-income countries
Limits	Published after 2000. English language.	Animal or laboratory studies.

2.2. Search strategy, selection of studies and data extraction.

Our search strategies are provided in Appendix A. The search was last executed in December 2022 in Medline (1946 to December 02, 2022), EMBASE (1974 to 2022 December 02), Maternity and Infant Health (1971 to November 08, 2022), and the IPD database.

The search has two facets: the outcome (prevalence of foetal alcohol spectrum disorder), and the exposure (drinking during pregnancy). The reference lists of reviews identified in our search were also scrutinised for potentially eligible studies.

All records were retrieved and entered into an EndNote library to remove duplicates, and then imported into Covidence for screening. We took a two-stage approach to screening. In the first stage, we reviewed titles and abstracts for relevance. In the second stage, we screened the full text of all potentially eligible studies. At both stages, two independent reviewers screened papers, with differences arbitrated by a third reviewer.

For the prevalence review, we extracted information on the country where the study was conducted, sample size, years of recruitment, sampling method, diagnostic guidelines, ascertainment method, method for collecting maternal drinking history and the extent to which ascertainment was blinded to maternal drinking history. For the dose-response review, we additionally extracted details on levels and patterns of drinking during pregnancy. One reviewer conducted data extraction with a random sample checked for accuracy by a second reviewer. As this is a scoping review, we did not conduct quality assessment of the included studies.

2.3. Results

2.3.1. Studies identified.

3,759 unique records were screened at the title and abstract stage, and we reviewed 196 full-text articles, finding 37 eligible articles. Of these, 20 reported prevalence estimates and 17 reported a dose-response relationship; no studies reported both.

2.3.2. Characteristics of included studies.

2.3.2.1. Prevalence studies.

Most studies identified were conducted in the Americas region (n=9),[7-15] followed by the European region (n=8)[16-23] and the Western Pacific region (n=3)[24-26]. Most studies (n=11)[9-15, 18, 19, 21, 23] used a cross sectional design, five studies[16, 17, 20, 25, 26] were retrospective registry

based, and three[7, 8, 24] used passive surveillance. Only one study[22] was based on a prospective cohort.

Figure 1: PRISMA-ScR flow diagram.

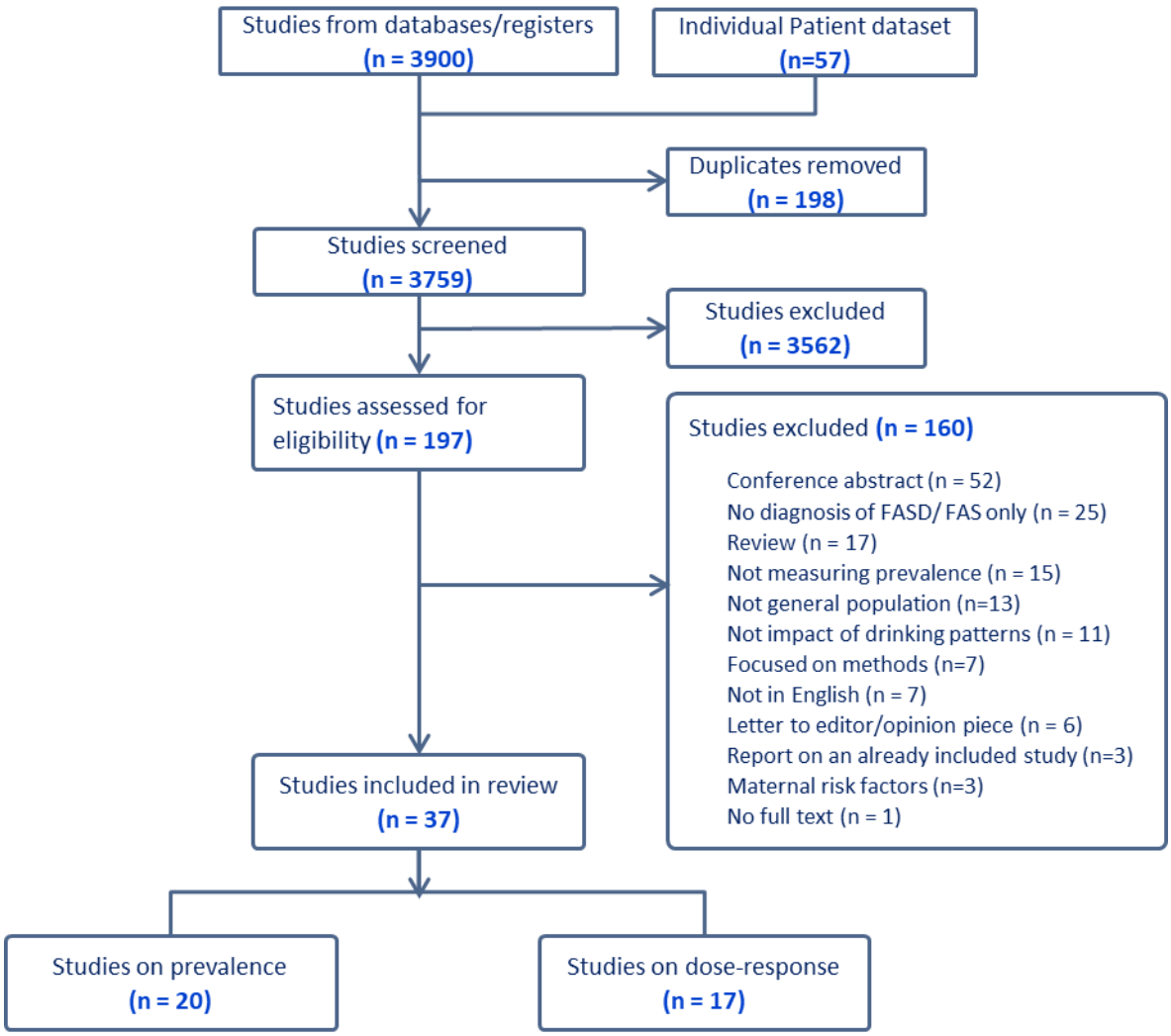


Table 2 reports the characteristics of the included prevalence studies. The US Institute for Medicine diagnostic criteria in different editions (1996,[27] 2005[28] and 2016[29]) were the most commonly used (n=7).[11-14, 18, 19, 24] This was followed by the most recent 2016 FASD Canadian guidelines,[30] (n=4),[9, 21-23] and the 4-digit diagnostic code[31] (n=2).[15, 25] The remaining studies each used a different diagnostic guideline (n=7).[7, 8, 10, 16, 17, 20, 26]

Regarding the age of children included in the studies, 12 studies[8-15, 18, 19, 21, 23] evaluated children between the ages of four and nine years old, five studies[7, 22, 24-26] included a wide range of ages from newborns to 17 years old, two studies[16, 17] included only children under one year old, and one does not report the age of children included.[20]

Prevalence figures ranged from 0.0058 (95% CI 0.0046-0.0071)[24] to 170 (95% CI 161-178)[22] per 1,000 population.

In Box 1 we summarise the characteristics of two important and influential UK studies: one based on the ALSPAC cohort study, and one school-based case ascertainment study carried out in the Greater Manchester area. The methods, strengths and limitations of these study designs are discussed further in section 3, where we report our expert roundtable discussions.

Table B1, in Appendix B, reports the sampling and methods for collecting data on drinking during pregnancy in the included studies.

BOX 1: INFLUENTIAL ENGLISH STUDIES OF FASD PREVALENCE – SUMMARY OF METHODS AND FINDINGS

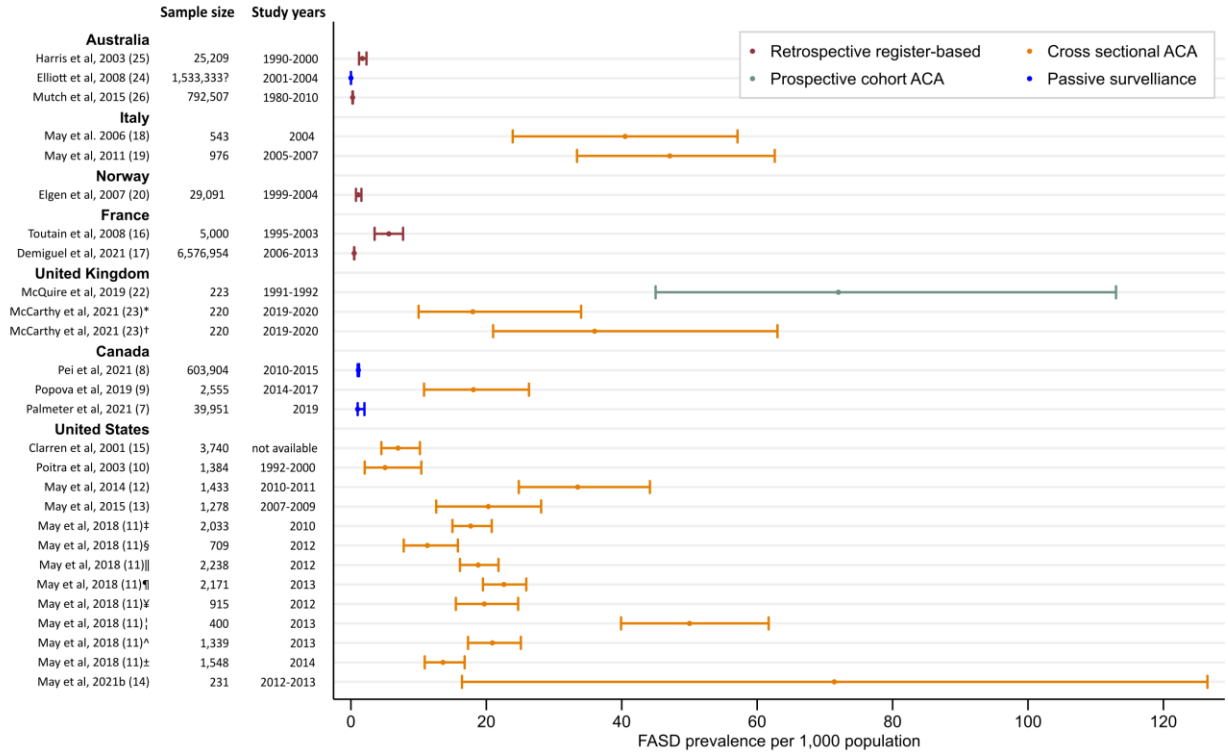
Avon Longitudinal Study of Parents and Children (ALSPAC) – birth cohort study (McQuire et al 2019)[22]

- Used data from a prospective population-based birth-cohort study, which recruited 14,541 pregnant women from the Bristol area in 1991 to 1992.
- Measured drinking repeatedly during pregnancy, which reduces any recall bias, but reporting bias remains. The researchers classified prenatal alcohol exposure into categories based on timing, volume and binge drinking, with 'any', 'mid' and 'strict' categories corresponding to increasing levels of exposure (dose and/or duration).
- Used the 2005 Canadian diagnostic guidelines to develop a screening algorithm for FASD using relevant ALSPAC measures. These measures included growth (weight, height, BMI), facial features, and central nervous system (CNS) measures such as co-ordination tests, any seizures, cerebral palsy, head circumference, tests of cognition, memory, communication, academic achievement, neurodiversity and emotional and behavioural difficulties. The algorithm was validated by an expert case-conference panel (including a psychiatrist, paediatrician and educational psychologist) considering a stratified random sample of 31 participant profiles to decide whether, on the balance of probability, a diagnosis of FASD would be made in clinic, given the information provided.
- Repeated measurement – at birth, age 7, and school transition points, up to age 15.
- Estimated prevalence using the complete case sample (n=223) was 72 per 1000 (95% CI 45-113), using single imputation (n=13,495) it was 60 per 1000 (95% CI 57-65) and using multiple imputation (n=13,495) it was 170 per 1000 (95% CI 161-178)

Greater Manchester study (McCarthy et al 2021)[23]

- Cross-sectional case ascertainment study
- Diagnosis using the 2016 Canadian guidelines.
- All children who were consented (n=220) were screened in three mainstream schools
- After initial screening, 47 were invited to further screening, of whom 23 (plus 3 opt-ins) were screened.
- Drinking measures – retrospective maternal survey at age 8-9
- Estimated prevalence: 18 per 1000 (95% CI 10-34) including confirmed cases, and 36 per 1000 (95% CI 21-63) for possible cases.

Figure 2: Prevalence of FASD reported by the included studies.



*analysis of confirmed FASD cases; †: analysis of confirmed and possible cases of FASD; ‡: analysis of sample 1 from Mid-western region; §: analysis of sample 2 from Mid-western region; ‖: analysis of sample 1 from Pacific Southwestern region; ¶: analysis of sample 2 from Pacific Southwestern region; ¥: analysis of sample 1 from Rocky Mountains region; ¦: analysis of sample 2 from Rocky Mountains region; ^: analysis of sample 1 from Southeastern region; ±: analysis of sample 2 from Southeastern region.

2.3.2.2. Studies reporting dose-response and drinking patterns.

Table 3 reports the characteristics of the included studies of dose-response and drinking patterns. Most of the studies identified were conducted in the African region (n=8),[14, 32-38] followed by the Americas (n=4)[39-42] and Europe (n=3).[43-45] One study[46] compared a sample from South Africa and another from the United States. Only one study was conducted in the Western Pacific region (Australia).[47] Most studies (n=11)[32-37, 40, 42, 45, 46, 48] used a cross sectional design, while three studies[41, 44, 47] were registry based and another three[38, 39, 43] were prospective cohorts.

Table B2 in appendix B reports sampling methods and diagnostic criteria used in the included studies.

Similarly to the prevalence review, in the dose-response and drinking patterns studies, the US Institute for Medicine diagnostic criteria in its different editions were the most used (n=12).[32-38, 40, 45-48] Five studies[39, 41-44] each used a different diagnostic guideline (Table B2). Methods of measuring the exposure to alcohol are also summarised in Table 4. Most studies

(n=12)[32-38, 40, 41, 45, 46, 48] reported whether the participant drank at any point during the pregnancy followed by measures of quantity expressed as either drinks per drinking day (n=7)[34-37, 40, 46, 48] or average number of drinks per week (n=4).[32, 34, 35, 43]

Details of the findings of the included studies are in Table 5 and Table 6. This presents a complex picture, involving differing methods, drinking measures and FASD diagnosis thresholds, making the findings impossible to synthesise in any meaningful way. Some studies aggregate children with FASD, while some classify outcomes into FAS, partial FAS (pFAS) or alcohol-related neurodevelopmental disorder (ARND). Mothers are then questioned in very different ways about their drinking habits during pregnancy (some specifically before they recognised that they were pregnant, and some specifying trimesters).

In Table 5, perhaps the easiest dose-response studies to interpret are those that asked mothers how much they drank per drinking day and presented the odds of FASD for each group. For example, May et al 2022b[46] demonstrated a clear dose-response relationship, with odds of FASD (compared with no drinking) of 2.6 (95% CI 1.1-6.0) for 1 drink per drinking day, rising steadily to an odds ratio of 12.1 (95% CI 9.3-15.7) for 5 or more drinks per drinking day. This analysis did not, however, account for the frequency of drinking days. Not all such studies demonstrate this linear association. May et al 2021b[48] reports that in their sample, 2 drinks per drinking day has the highest odds of FASD, while May et al 2022a[37] and Chambers et al 2019[40] report that 4 drinks per drinking day has the highest odds of FASD. The certainty of these estimates is low because they have very wide confidence intervals.

In Table 6, relating FASD to drinking behaviour by pregnancy trimester shows a similarly complex picture of differing measures and outcomes. Interpreting this data is challenging, and formal synthesis is inappropriate. For example, in May et al 2016b[35] the authors report asking women about their drinking during pregnancy in terms of drinks per week, drinking days, drinks per drinking day, number of drinking days, drinks per occasion, episodes of binge drinking and timing (by trimester). May et al 2013[33] report odds of FASD of 12.2 (95% CI 4.1-35.9) for drinking during the first trimester compared with no drinking, odds of 60.8 (12.7-291.4) for drinking during the first and second trimester compared with no drinking and odds of 64.8 (23.3-180.1) for drinking throughout the pregnancy compared with no drinking. Later studies, also mostly by May and colleagues, show a very similar pattern (although different odds ratios). Drinking throughout pregnancy increases risks, but drinking in any one trimester increases the odds of FASD significantly compared with no drinking. This supports the current policy guidance recommending abstinence throughout pregnancy, particularly in terms of clarity of message.

Table 2 Characteristics of included studies reporting FASD prevalence estimates.

Source	Country (State/ Province/ Territory)	Study year(s)	Study design	Sample size	N of FASD cases	Analysis	Prevalence (95% CI) per 1,000 population	Diagnostic guidelines/ Case definition	Age range (years)	Method
European Region										
Toutain et al, 2008[16]	France	1995-2003	Retrospective registry based	5000	28	All live births between 1995 and 2003	5.6 (3.5 - 7.7)	Guidelines established by the Fetal Alcohol Study Group of the RSA	0-1 (Newborns)	Clinic-based
Demiguel et al, 2021[17]	France (and French overseas territories except Mayotte)	2006-2013	Retrospective registry based	6,576,954	3207	All children with a hospital stay in the first 28 days of life	0.49 (0.47 - 0.51)	ICD codes Q86.0 (FAS) or P04.3 (CAE)	first 28 days	PS
May et al, 2006[18]	Italy (Lazio)	2004	Cross-sectional	543	22	All screened children as denominator	40.5 (23.9 - 57.1)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
May et al. 2006[18]	Italy (Lazio)	2004	Cross-sectional	1086	22	All children attending selected classes	20.3 (11.9 - 28.6)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
May et al, 2011[19]	Italy (Lazio)	2005-2007	Cross-sectional	1988	46	All children attending selected classes	23.1 (17 - 30.7)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
May et al, 2011[19]	Italy (Lazio)	2005-2007	Cross-sectional	976	46	All screened children as denominator	47.1 (33.4 - 62.6)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
Elgen et al, 2007[20]	Norway (Hordaland)	1999-2004	Retrospective registry based	29091	32	Children born at Haukeland University Hospital	1.1 (0.75 - 1.55)	CDC diagnostic guidelines	NA	Clinic-based
Okulicz-Kozaryn et al, 2017[21]	Poland (South East)	2012	Cross-sectional	2500 (first assessment: 409; full assessment: 280)	50	Original sample as denominator	20 (14.9 - 26.3)	FASD Canadian guidelines for diagnosis (2016)	7 to 9	ACA
McQuire et al, 2019[22]	United Kingdom (Bristol area)	1991-1992	Prospective cohort	223	16	Complete case	72 (45 - 113)	FASD Canadian guidelines for diagnosis (2016)	0 to 15	ACA

Source	Country (State/ Province/ Territory)	Study year(s)	Study design	Sample size	N of FASD cases	Analysis	Prevalence (95% CI) per 1,000 population	Diagnostic guidelines/ Case definition	Age range (years)	Method
McQuire et al, 2019[22]	United Kingdom (Bristol area)	1991-1992	Prospective cohort	13,495	2294	Single imputation	60 (57 - 65)	FASD Canadian guidelines for diagnosis (2016)	0 to 15	ACA
McQuire et al, 2019[22]	United Kingdom (Bristol area)	1991-1992	Prospective cohort	13,495	2294	Multiple imputation	170 (161 - 178)	FASD Canadian guidelines for diagnosis (2016)	0 to 15	ACA
McQuire et al, 2019[22]	United Kingdom (Bristol area)	1991-1992	Prospective cohort	13,495	2294	Revised CNS criteria+ any PAE	128 (120 - 135)	FASD Canadian guidelines for diagnosis (2016)	0 to 15	ACA
McCarthy et al, 2021[23]	United Kingdom (Manchester)	2019-2020	Cross-sectional	220	4	FASD	18 (10 - 34)	FASD Canadian guidelines for diagnosis (2016)	8 to 9	ACA
McCarthy et al, 2021[23]	United Kingdom (Manchester)	2019-2020	Cross-sectional	220	8	FASD+possible FASD	36 (21 - 63)	FASD Canadian guidelines for diagnosis (2016)	8 to 9	ACA
Region of the Americas										
Palmeter et al, 2021[7]	Canada	2019	Passive surveillance	39,951	54	FASD	1 (1 - 2)	Respondent answered "yes" to the question: "Has this child been diagnosed with any of the following long-term conditions? – Fetal Alcohol Spectrum Disorder, also known as FASD."	1 to 17	PS
Pei et al, 2021[8]	Canada	2010-2015	Passive surveillance	603,904	658	FASD	1.1 (1 - 1.2)	Teacher-reported FASD diagnosis through the Early Development Instrument (EDI) a 103-item teacher-completed measure of children's development at school entry	4 to 6	PS

Source	Country (State/ Province/ Territory)	Study year(s)	Study design	Sample size	N of FASD cases	Analysis	Prevalence (95% CI) per 1,000 population	Diagnostic guidelines/ Case definition	Age range (years)	Method
Popova et al, 2019[9]	Canada (Greater Toronto Area in Ontario)	2014-2017	Cross-sectional	2,555	21		18.1 (10.8 - 26.3)	FASD Canadian guidelines for diagnosis (2016)	7 to 9	ACA
Popova et al, 2019[9]	Canada (Greater Toronto Area in Ontario)	2014-2017	Cross-sectional	2,555	21	Sensitivity analysis (assuming non-consented children had a similar rate of FASD to that of the random sample)	29.3 (12.4 - 56.2)	FASD Canadian guidelines for diagnosis (2016)	7 to 9	ACA
Poitra et al, 2003[10]	United States	1992-2000	Cross-sectional	1,384	7	All screened children as denominator	5.05 (2.04 - 10.4)	Criteria by Sokol and Clarren	5 to 6	ACA
May et al, 2018[11]	United States (Midwestern)	2010	Cross-sectional	2,033	36	Sample 1	17.7 (15 - 20.8)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	first-grade children	ACA
May et al, 2018[11]	United States (Midwestern)	2012	Cross-sectional	709	8	Sample 2	11.3 (7.8 - 15.8)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	first-grade children	ACA
May et al, 2018[11]	United States (Pacific Southwestern)	2012	Cross-sectional	2,238	42	Sample 1	18.8 (16.1 - 21.8)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	first-grade children	ACA
May et al, 2018[11]	United States (Pacific Southwestern)	2013	Cross-sectional	2,171	49	Sample 2	22.6 (19.5 - 25.9)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	first-grade children	ACA
May et al, 2018[11]	United States (Rocky Mountain)	2012	Cross-sectional	915	18	Sample 1	19.7 (15.5 - 24.7)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	first-grade children	ACA

Source	Country (State/ Province/ Territory)	Study year(s)	Study design	Sample size	N of FASD cases	Analysis	Prevalence (95% CI) per 1,000 population	Diagnostic guidelines/ Case definition	Age range (years)	Method
May et al, 2018[11]	United States (Rocky Mountain)	2013	Cross-sectional	400	20	Sample 2	50 (39.9 - 61.7)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	first-grade children	ACA
May et al, 2018[11]	United States (Southeastern)	2013	Cross-sectional	1,339	28	Sample 1	20.9 (17.3 - 25.1)	The Revised IOM diagnostic guidelines for FASD	first-grade children	ACA
May et al, 2018[11]	United States (Southeastern)	2014	Cross-sectional	1,548	21	Sample 2	13.6 (10.9 - 16.8)	The Revised IOM diagnostic guidelines for FASD	first-grade children	ACA
May et al, 2014[12]	United States (Midwestern)	2010-2011	Cross-sectional	2,033	48	Prevalence assuming non-consented did not have FASD	23.6 (17.45 - 31.18)	The Revised IOM diagnostic guidelines for FASD	first-grade children	ACA
May et al, 2014[12]	United States (Midwestern)	2010-2011	Cross-sectional	1,433	48	Prevalence consented participants	33.5 (24.8 - 44.16)	The Revised IOM diagnostic guidelines for FASD	first-grade children	ACA
May et al, 2014[12]	United States (Midwestern)	2010-2011	Cross-sectional	196	16	Prevalence random controls	81.6 (43.3 - 119.9)	The Revised IOM diagnostic guidelines for FASD	first-grade children	ACA
May et al, 2014[12]	United States (Midwestern)	2010-2011	Cross-sectional	2,033	97	Prevalence consented + prevalence of random sample for non-consented	47.7 (38.5 - 56.9)	The Revised IOM diagnostic guidelines for FASD	first-grade children	ACA
May et al, 2015[13]	United States (Rocky Mountain)	2007-2009	Cross-sectional	2,377	26	Prevalence assuming non-consented did not have FASD	10.9 (6.76 - 15.1)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
May et al, 2015[13]	United States (Rocky Mountain)	2007-2009	Cross-sectional	1,278	26	Prevalence consented participants	20.3 (12.6 - 28.1)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
May et al, 2015[13]	United States (Rocky Mountain)	2007-2009	Cross-sectional	1,099	34	Prevalence random controls	30.9 (6.6 - 55.3)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA

Source	Country (State/ Province/ Territory)	Study year(s)	Study design	Sample size	N of FASD cases	Analysis	Prevalence (95% CI) per 1,000 population	Diagnostic guidelines/ Case definition	Age range (years)	Method
May et al, 2015[13]	United States (Rocky Mountain)	2007-2009	Cross-sectional	2,377	60	Prevalence consented +random sample prevalence for non-consented	25.2 (18.9 - 31.5)	The Revised IOM diagnostic guidelines for FASD	6 to 7	ACA
May et al, 2021b[14]	United States (Southeastern)	2012-2013	Cross-sectional	231	6	84 as denominator (everyone with a complete assessment)	71.4 (16.4 - 126.5)	The Revised IOM diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016	7 to 9	ACA
Clarren et al, 2001[15]	United States (Washington State)	Not available	Cross-sectional	3,740	26	All screened children as denominator	6.95 (4.5 - 10.2)	4-Digit diagnostic code	6 to 7	ACA
Western Pacific Region										
Elliott et al, 2008[24]	Australia	2001-2004	Passive surveillance	1,533,333	92		0.0058 (0.0046 - 0.0071)	IOM criteria	0 to 15	PS
Harris et al, 2003[25]	Australia (Northern Territory)	1990-2000	Retrospective registry based	25,209	43	Charts with specific ICD-9 and ICD-10 codes divided by all live births	1.7 (1.2 - 2.3)	Adapted 4-digit diagnostic code and the criteria by the AAP	0 to 10	Mixed methods (PS and clinic-based)
Mutch et al, 2015[26]	Australia (Western Australia)	1980 to 2010	Retrospective registry based	792,507	210		0.26 (0.23 - 0.3)	ICD-9 code 75992		PS

Abbreviations: ACA, active case ascertainment; AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; FAS: Foetal Alcohol Syndrome; FASD, foetal alcohol spectrum disorder; IOM, Institute of Medicine; NA, not available; PS: Passive Surveillance; RSA, Research Society on Alcoholism

Table 3 Characteristics of studies measuring a dose-response relationship between alcohol drinking during pregnancy and offspring with FASD.

Author	Country	Study year(s)	Sample Size	Drinking measure	Consumption measure	Collection periods	Prospective/ retrospective	Drinking categories
African region								
May et al, 2007[32]	South Africa	1996-1999	FASD = 61, control = 133	Quantity and timing	Drinking (Yes/No) Average Number of drinks per week	Before Pregnancy During Pregnancy Trimesters	Retrospective	Drank during index pregnancy 1st Trimester 2nd Trimester 3rd Trimester Average No. drinks per week
May et al, 2013[33]	South Africa	2011	250	Drink Alcohol (Yes/No) Frequency	Drinking (Yes/No) Drinking days	Trimesters	Retrospective	No drinking First Trimester only First and second trimester All Trimesters Third trimester only Number of drinking days per week
May et al, 2016a[34]	South Africa	2010-2011	FAS = 168 pFAS = 106 ARND = 59 Control = 212	Frequency, Quantity and timing	Drinking (Yes/No) Drinks per day Drinking days Binge	Trimesters	Retrospective	Drinking during pregnancy Avg # drinks per week (during pregnancy) Drinks per drinking day during pregnancy Consumed 3 drinks or more per occasion during pregnancy Consumed 5 drinks or more per occasion during pregnancy Current drinker Drinking before index pregnancy Drank during 1st trimester Drank during 2nd trimester Drank during 3rd trimester
May et al, 2016b[35]	South Africa	2010-2011	FAS = 68 pFAS = 89 ARND = 39 control = 207	Frequency, Quantity and timing	Drinking (Yes/No) Drinks per day Drinking days Binge	During pregnancy Trimesters	Retrospective	Drank during index pregnancy direct report (% Yes) Avg # drinks per week during pregnancy Avg # of drinking days during pregnancy

Author	Country	Study year(s)	Sample Size	Drinking measure	Consumption measure	Collection periods	Prospective/ retrospective	Drinking categories
								Consumed 3 drinks or more per occasion during pregnancy (%) Consumed 5 drinks or more per occasion during pregnancy (%) Drank during 1st trimester Binged 3+ Binged 5+ Avg # of drinks per drinking day # of drinking days per week Drank during 2nd trimester Binged 3+ Binged 5+
May et al, 2017[36]	South Africa	2011-2012	FAS = 118 pFAS=91 ARND=55 Control =100	Frequency, quantity, and timing	Drinking (Yes/No) Drinks per day Drinking days Binge	During pregnancy Trimesters	Retrospective	Drank during index pregnancy Average # drinks per day during pregnancy Consumed 3 drinks or more per occasion during pregnancy Consumed 5 drinks or more per occasion during pregnancy
May et al, 2021a[48]	South Africa	2014-2016	554	Quantity and timing	Drinking (Yes/No) Drinks per drinking day	First Trimester Trimesters	Retrospective	Trimester of Drinking 1st Trimester Only 1st and 2nd Trimester 1st, 2nd and 3rd Trimester Drinks per drinking day (1st trimester)
May et al, 2022a[37]	South Africa	2016-2017	303	Quantity	Drinking (Yes/No) Drinks per drinking day	Trimesters First Trimester	Retrospective	Trimester of Drinking 1st Trimester 2nd Trimester 3rd Trimester Drinks per drinking day (1st trimester)
May et al, 2022b[46]	South Africa	2008-2018	1925	Drink Alcohol (Yes/No) Quantity	Drink Alcohol (Yes/No) Drinks per drinking day	Trimesters First Trimester	Retrospective	Drinks per drinking day (1st trimester) Trimester of Drinking 1st Trimester Only 1st and 2nd Trimester 1st, 2nd and 3rd Trimester

Author	Country	Study year(s)	Sample Size	Drinking measure	Consumption measure	Collection periods	Prospective/ retrospective	Drinking categories
Wynn et al, 2020[38]	South Africa	2009-2010	977	Frequency, quantity and binge drinking	AUDIT C	During Pregnancy	Prospective	Drank during pregnancy baseline 60-month recall Binge>= once per month
European Region								
Kesmodel et al, 2019[43]	Denmark	1997-2008	n=366 (3 to 4 n=10, 1 to 2 n=356)	Frequency/ quantity	Average number of drinks per week Binge drinking	During Pregnancy	Prospective	Average number of drinks per week Binge drinking (Yes/No) Binge episodes
Mullaly et al, 2011[44]	Ireland	2005-2007	n=61241 never = 11613 low=43455 moderate=6059 high=114	Drinking level	Units per week - categorised into risk level	Prior to pregnancy and up until the pregnancy was confirmed	Retrospective	Units classified Never Low (0-5 units) Moderate (6-20 units) High (>20 units)
Petkovic et al, 2013[45]	Croatia	Not clear	n=824 FAS/pFAS=55	Quantity	Drinking (Yes/No)	Trimesters	Retrospective	1st trimester 2nd Trimester 3rd Trimester Entire pregnancy
Region of the Americas								
Barr et al, 2001[39]	United States	1974-1975 maternal cohort. 25-year follow up	1439	Frequency/ quantity	Other risk category	Before and during pregnancy	Prospective	Specified Criteria Criteria 1: Monthly frequency of 5 or more drinks and 1/4 monthly frequency of 3–4 drinks >=4 (Pre and/or During pregnancy) Criteria 2: Daily or almost daily drinking without meeting criteria 1 above (24 or more drinking occasions per month) (Pre and/ or During pregnancy) Criteria 3: Everyone else
Chambers et al, 2019[40]	United States (Pacific Southwest)	2012-2013	n = 854 FAS: 5 pFAS: 44 ARND: 44 No FASD: 761	Frequency/ quantity	Drinking days Drinks per drinking day	1. Before Pregnancy recognition (BPR) 2. After Pregnancy	Retrospective	Drank (Yes/No) Drinks per drinking Day Drinking days Every day or almost every day 3 to 4 times/wk 1 to 2 times/wk

Author	Country	Study year(s)	Sample Size	Drinking measure	Consumption measure	Collection periods	Prospective/ retrospective	Drinking categories
						Recognition (APR) during first trimester 3. Second trimester 4. Third trimester		2 to 3 times/month 1 times/month or less Drank in the past 30 days Max drinks/24 hours in the past 30 days
Kvigne et al, 2008[41]	United States (Northern Plains)	1981-1993	Study 1: FAS cases= 43; controls=86. Study 2: incomplete FAS=35; controls=70	Drink Alcohol (Yes/No)	Drinking (Yes/No)	Before and during pregnancy	Prospective	Drank (Yes/No)
May et al, 2022b[46]	United States	2009-2017	817	Drink Alcohol (Yes/No)	Drink Alcohol (Yes/No)	Trimesters	Retrospective	Trimester of Drinking 1st Trimester Only 1st and 2nd Trimester 1st, 2nd and 3rd Trimester
Popova et al, 2020[42]	Canada	2014-2017	All = 173 FASD =19 Deferred=5 Control =37	Risky drinking	Risk	Before Pregnancy recognition (BPR) After Pregnancy recognition (APR)	Retrospective	Alcohol use High risk Some risk No risk(no use)
Western Pacific Region								
O'Leary et al, 2010[47]	Australia	1995-1997	N=4714 Abstinent =919 Low=1555 Moderate=1289 Heavy=724	Drinking level	Risk	Before Pregnancy recognition (BPR) First Trimester Late pregnancy	Retrospective	Abstinent Low Moderate [Moderate or Binge Less Than Weekly] Heavy [Binge 1 or 2 times per wk; Binge 2 times per wk; Heavy (70.1–140.0 g/wk); Very Heavy (>140.1 g/wk)]

Table 4 Number of studies using each measure of drinking behaviour.

		Total no. of studies reporting measure	No. of studies reporting measure by trimester
Did you drink any alcohol?	Yes/No	12	10
Quantity	Average number of drinks per week	4	0
	Average number of drinks per day	1	0
	Units per week	1	0
	Drinks per drinking day	7	4
Frequency	Drinking Days per week	4	3
	Drinking days, (categorised daily, per week, per month)	2	2
Binge drinking	Yes/No	5	3
	Number of binge episodes	1	0
Other risk classification		3	1

Table 5 Drinking behaviour during pregnancy and its association with an FASD diagnosis.

Author, year	Quantity, frequency or timing	FAS*	pFAS*	ARND*	No FASD
Did you drink any alcohol? Yes/No					
Chambers et al, 2019[40]	Before pregnancy recognition (BPR), % Yes (n Yes/ all)	40.0 (2/5)	57.9 (22/38)	100 (31/31)	21.4 (154/720)
Kvigne et al, 2008[41]	During pregnancy, % Yes (n Yes/all)	100 (43/43)			19.7 (17/86)
May et al, 2017[36]	During pregnancy, % Yes (n Yes/all)	84.9 (100/118)	69.8 (64/91)	100 (55/55)	45 (45/100)
May et al, 2016a[34]	During pregnancy, % Yes (n Yes/all)	92.4 (133/145)	81.6 (80/98)	90.9 (50/55)	28.5 (59/207)
May et al, 2016b[35]	During pregnancy, % Yes (n Yes/all)	89.7 (61/68)	70.6 (63/89)	100 (39/39)	41.1 (85/207)
May et al, 2007[32]	During pregnancy, % Yes (n Yes/all)	95.5 (58/61)			24.2 (32/133)
	No FASD mothers, OR (95% CI)	1.0			
	During pregnancy, OR (95% CI)	65.6 (17.9–285.1)			
May et al, 2007[32]	During pregnancy, % Yes (n Yes/all)	96 (53/55)	93.8 (17/18)	-	24.2 (32/133)
May et al, 2021a[32]	During pregnancy, % Yes (n Yes/all)	85.1 (41/48)	85.1 (55/65)	100 (67/67)	37.3 (44/117)
Petkovic et al, 2013[45]	During pregnancy, % Yes (n Yes/all)	5.5 (3/55)		-	2.5 (19/769)
Wynn et al, 2020[38]	During pregnancy - baseline, % Yes (n Yes/ all)	88.9% (16/18) + possible 26.1% (37/142)			25.1 (205/817)
Wynn et al, 2020[38]	During pregnancy - 60-month recall, % Yes (n Yes/ all)	83.3% (15/18) + possible 19.7% (28/142)			19.1 (142/817)
Quantity - Average number of drinks					
Kesmodel et al, 2019[43]	0 vs 1 to 4 per week, OR (95% CI)	8.5 (6.03 to 12.0)			
May et al, 2007[32]	per week, Mean (SD)	13.0 (13.6)	4.9 (3.45)	-	6.0 (7.71)
May et al, 2016a[34]	per week, Mean (SD)	16.2 (20.0)	11.4 (19.5)	8.5 (9.8)	2.7 (8.9)
May et al, 2016b[35]	per week, Mean (SD)	16.5 (23.2)	4.5 (8.1)	8.4 (13.5)	2.3 (6.2)
May et al, 2017[36]	per day, Mean (SD)	5.9 (5.8)	2.9 (4.3)	6.1 (5.9)	1.7 (3.4)
Chambers et al, 2019[40]	BPR, Mean (SD)	3.0 (0)	2.8 (2.1)	6 (19.4)	9 (5.8)
May et al, 2021a[48]	After pregnancy recognition, Mean (SD)	5.1 (5.9)	2.8 (4.1)	2.6 (4.2)	0.7 (3.0)
Quantity – Units					
Mullaly et al, 2011[44]	Never, n	0	-		11613
Mullaly et al, 2011[44]	Low 0-5 units per week, n	1	-		43454
Mullaly et al, 2011[44]	Moderate 6-20 units per week, n	1	-		6058
Mullaly et al, 2011[44]	High >20 units per week, n	1	-		113
Quantity - Drinks per drinking day					
Chambers et al, 2019[40]	None	1.0			
	1 drink per drinking day, OR (95% CI)	3.8 (1.6, 8.4)			
	2 drinks per drinking day, OR (95% CI)	7.7 (3.3, 17.3)			
	3 drinks per drinking day, OR (95% CI)	24.9 (11.2, 56.5)			
	4 drinks per drinking day, OR (95% CI)	25.4 (7.2, 90.2)			
	5 drinks per drinking day, OR (95% CI)	15.1 (5.3, 41.0)			
May et al, 2022a[37]	None	1.0			
	1 drink per drinking day, OR (95% CI)	3.6 (0.8, 16.2)			
	2 drinks per drinking day, OR (95% CI)	5.9 (2.0, 17.7)			
	3 drinks per drinking day, OR (95% CI)	5.9 (1.4, 24.9)			
	4 drinks per drinking day, OR (95% CI)	38.3 (9.9, 148.6)			
	5 or more drinks per drinking day, OR (95% CI)	19.8 (9.4, 41.8)			
May et al, 2022b[46]	None	1.0			
	1 drink per drinking day, OR (95% CI)	2.6 (1.1, 6.0)			

Author, year	Quantity, frequency or timing	FAS*	pFAS*	ARND*	No FASD
	2 drinks per drinking day, OR (95% CI)	4.1 (2.46, 6.9)			
	3 drinks per drinking day, OR (95% CI)	5.0 (3.4, 7.2)			
	4 drinks per drinking day, OR (95% CI)	8.7 (5.3, 14.3)			
	5 or more drinks per drinking day, OR (95% CI)	12.1 (9.3, 15.7)			
May et al, 2017[36]	3 drinks or more per occasion, % Yes (n Yes/all)	73.7 (87/118)	53.8 (49/91)	94.2 (52/55)	34 (34/100)
May et al, 2017[36]	5 drinks or more per occasion, % Yes (n Yes/all)	65.3 (77/118)	39.6 (36/91)	57.7 (32/55)	26 (26/100)
May et al, 2016a[34]	Drinks per drinking day, Mean (SD)	6.5 (7.9)	4.1 (5.1)	3.5 (3.5)	0.90 (2.8)
May et al, 2016a[34]	3 drinks or more per occasion, % Yes (n Yes/all)	84.0 (122/144)	71.4 (70/98)	78.6 (44/56)	23.5 (46/196)
May et al, 2016a[34]	5 drinks or more per occasion, % Yes (n Yes/all)	66.0 (96/144)	58.2 (57/98)	46.4 (26/56)	14.3 (28/196)
May et al, 2016b[35]	3 drinks or more per occasion, %	73.5 (50/68)	47.2 (42/89)	89.7 (35/39)	27.1 (56/207)
May et al, 2016b[35]	5 drinks or more per occasion, %	66.2 (45/68)	32.6 (29/89)	53.8 (21/39)	17.9 (37/207)
May et al, 2021a[48]	None	1.0			
	1 drink per drinking day, OR (95% CI)	1.8 (0.3, 12.2)			
	2 drinks per drinking day, OR (95% CI)	13.0 (1.3, 133.4)			
	3 drinks per drinking day, OR (95% CI)	9.4 (1.9, 33.6)			
	4 drinks per drinking day, OR (95% CI)	8.0 (1.2, 41.5)			
	5 or more drinks per drinking day, OR (95% CI)	7.0 (6.1, 25.8)			
Frequency - Drinking days per week					
May et al, 2013[33]	During Pregnancy, Mean (SD)	2.3 (1.2)	1.8 (1.1)	1.9 (1.1)	1.0 (0.6)
May et al, 2017[36]	Average # of drinking days, Mean (SD)	1.7 (1.6)	0.8 (1.0)	1.5 (1.4)	0.4 (0.7)
May et al, 2016b[35]	Average # of drinking days, Mean (SD)	1.9 (1.9)	0.8 (1.1)	1.6 (1.3)	0.4 (.8)
Chambers et al, 2019[40]	BPR – Everyday, n (%)	0 (0.0)	3 (13.6)	6 (19.4)	9 (5.8)
Frequency - Drinking days (categorised daily, per week, per month)					
Chambers et al, 2019[40]	BPR - 3 to 4 times/wk, % Yes (n Yes/all)	0 (0/2)	22.7 (5/22)	25.8 (8/31)	7.1 (11/155)
Chambers et al, 2019[40]	BPR - 1 to 2 times/wk, % Yes (n Yes/all)	0 (0/2)	31.8 (7/22)	22.6 (7/31)	28.6 (44/154)
Chambers et al, 2019[40]	BPR - 2 to 3 times/ month, % Yes (n Yes/all)	0 (0/2)	9.1 (2/22)	29 (9/31)	11.7 (18/154)
Chambers et al, 2019[40]	BPR - 1 times/month or less, % Yes (n Yes/all)	100 (2/2)	22.7 (5/22)	3.2 (1/31)	46.8 (72/154)
Binge drinking – Yes/No					
Kvigne et al, 2008[41]	Cases vs controls, OR (95% CI)	12.00 (2.76, 110.39)			
Wynn et al, 2020[38]	Binge ≥ once per month – baseline, % Yes (n Yes/all)	66.7% (12/18) + possible 13.4% (31/142)			13.5% (100/817)
Wynn et al, 2020[38]	Binge ≥ once per month - 60-month recall, % Yes (n Yes/all)	66.7% (12/18) + possible 14.1% (32/142)			16.2% (120/817)
Kesmodel et al, 2019[43]	Any binge drinking, OR (95% CI)	1.4 (1.0 to 1.8)			
Binge drinking - Number of binge episodes					
Kesmodel et al, 2019[43]	one vs zero, OR (95% CI)	1.9 (1.5 to 2.5)			
Other risk classification					
Popova et al, 2020[42]	BPR- High risk, n (%)	12 (63.2)			0 (0.0)
	BPR- Some risk, n (%)	7 (36.8)			25 (67.6)
	BPR- No risk (no use), n (%)	0 (0.0)			12 (32.4)
Popova et al, 2020[42]	APR- High risk, n (%)	0 (0.0)			0 (0.0)
	APR- Some risk, n (%)	2 (10.5)			2 (5.4)

Author, year	Quantity, frequency or timing	FAS*	pFAS*	ARND*	No FASD
	APR- No risk (no use), n (%)	17 (89.5)			35 (94.6)
Barr et al, 2001[39]	Criteria 1: Monthly frequency of 5 or more drinks and 1/4 monthly frequency of 3–4 drinks >=4 during pregnancy, % Yes (n Yes/ all)	38.4 (28/73)			61.6 (45/73)
Barr et al, 2001[39]	Criteria 2: Daily or almost daily drinking without meeting criteria 1 above (24 or more drinking occasions per month) during pregnancy, % Yes (n Yes/all)	8.1 (8/99)			91.9 (91/99)
Barr et al, 2001[39]	Criteria 3: Everyone else, % Yes (n Yes/ all)	0			100 (1267/1267)
		ARBD—alcohol-related birth defect			No Birth Defect
O'Leary et al, 2010[47]	Abstinent throughout pregnancy, n (%)	10 (1.1)			859 (93.5)
O'Leary et al, 2010[47]	Low, n (%)	16 (1.0)			1450 (93.2)
O'Leary et al, 2010[47]	Moderate - <70g/week or binge less than weekly, n (%)	13 (0.9)			1433 (94.5)
O'Leary et al, 2010[47]	Heavy - > 70 g/week or binge 1 or more times per week, n (%)	12 (1.7)			667 (92.1)
O'Leary et al, 2010[47]	Abstinent	1.0			
	Low, aOR (95% CI)	0.97 (0.44–2.17)			
	Moderate - <70g/week or binge less than weekly, aOR (95% CI)	0.80 (0.34–1.85)			
	Heavy - > 70 g/week or binge 1 or more times per week, aOR (95% CI)	1.54 (0.63–3.75)			

Abbreviations: Foetal alcohol Syndrome (FAS); Partial Foetal Alcohol Syndrome (pFAS); Alcohol-Related Neurodevelopmental Disorder (ARND); Foetal Alcohol Spectrum Disorders (FASD); Alcohol-Related Dirth Defect (ARBD); Before pregnancy recognition (BPR); After Pregnancy recognition (APR).

Table 6 Drinking behaviour by trimester of pregnancy and its association with an FASD diagnosis.

Author, year	Quantity, frequency, or timing	FAS	pFAS	ARND	No FASD
Did you drink any alcohol? Yes/No					
Chambers et al, 2019[40]	After pregnancy recognition (APR) - First trimester, % Yes (n Yes/all)	0 (0/5)	7.9 (3/38)	27.0 (10/37)	2.9 (21/724)
Chambers et al, 2019[40]	Second trimester, % Yes (n Yes/all)	0 (0/5)	7.9 (3/38)	22.2 (8/36)	5.2 (38/731)
Chambers et al, 2019[40]	Third trimester, % Yes (n Yes/all)	0 (0/5)	10.5 (4/38)	27.8 (10/36)	6.1 (44/721)
Chambers et al, 2019[40]	Third trimester-Drank in the past 30 days, % Yes (n Yes/all)	20.0 (1/5)	50.0 (19/38)	61.3 (19/31)	42.2 (304/720)
May et al, 2013[33]	First trimester only vs. no drinking, OR (95% CI)	12.2 (4.1, 35.9)			
May et al, 2013[33]	First and second trimesters only vs. no drinking, OR (95% CI)	60.8 (12.7, 291.4)			
May et al, 2013[33]	All trimesters vs. no drinking, OR (95% CI)	64.8 (23.3, 180.1)			
May et al, 2013[33]	Third trimester only vs. no drinking, OR (95% CI)	6.1 (0.4, 103.3)			
May et al, 2013[33]	First and second trimesters vs. first trimester only, OR (95% CI)	5.0 (0.9, 27.7)			
May et al, 2013[33]	All trimesters vs. first trimester only, OR (95% CI)	5.3 (1.6, 18.3)			
May et al, 2013[33]	All trimesters vs. first and second trimesters only, OR (95% CI)	1.1 (0.2, 5.7)			
May et al, 2022a[37]	Abstinence	1.0			
	First trimester (SA), OR (95% CI)	8.4 (4.1, 17.1)			
	Second trimester (SA), OR (95% CI)	17.7 (7.5, 42.0)			
	Third trimester (SA), OR (95% CI)	18.6 (7.594, 45.716)			
May et al, 2022b[46]	Abstinence	1.0			
	First trimester (SA), OR (95% CI)	4.6 (3.5, 6.0)			
	Second trimester (SA), OR (95% CI)	11.6 (8.2, 16.4)			
	Third trimester (SA), OR (95% CI)	15.4 (11.6, 20.5)			
	First trimester (USA), OR (95% CI)	7.7 (3.7,16.1)			
	Second trimester (USA), OR (95% CI)	2.4 (0.5, 12.6)			
	Third trimester (USA), OR (95% CI)	8.2 (2.9, 23.2)			
May et al, 2017[36]	First trimester, % Yes (n Yes/all)	81.0 (96/118)	67 (61/91)	100 (55/55)	43 (43/100)
	Second trimester, % Yes (n Yes/all)	71.4 (84/118)	45.2 (41/91)	83.3 (46/55)	25 (25/100)
	Third trimester, % Yes (n Yes/all)	60.6 (72/118)	24.5 (22/91)	59.3 (33/55)	13.1 (13/100)
May et al, 2016a[34]	First trimester, % Yes (n Yes/all)	91.0 (131/144)	81.6 (80/98)	90.9 (50/55)	28.0 (58/149)
	Second trimester, % Yes (n Yes/all)	80.0 (116/145)	61.2 (60/98)	67.3 (37/55)	15.0 (31/207)
	Third trimester, % Yes (n Yes/all)	68.3 (99/145)	49.0 (48/98)	59.3 (32/54)	12.1 (25/207)
May et al, 2016b[35]	First trimester, % Yes (n Yes/all)	76.5 (52/68)	55.1 (49/89)	92.3 (36/39)	37.2 (77/207)
	Second trimester, % Yes (n Yes/all)	64.7 (44/68)	38.2 (34/89)	69.2 (27/39)	18.8 (39/207)
	Third trimester, % Yes (n Yes/all)	44.1 (30/68)	22.5 (20/89)	41 (16/39)	9.2 (19/207)
May et al, 2007[32]	First trimester, % yes	93.9 (57/61)			23.3 (31/133)

Author, year	Quantity, frequency, or timing	FAS	pFAS	ARND	No FASD
May et al, 2007[32]	First trimester, OR (95% CI)	51.0 (15.9–181.9)			
May et al, 2007[32]	Second trimester, % yes	83.6 (51/61)			16.5 (22/133)
May et al, 2007[32]	Second trimester, OR (95% CI)	25.7 (10.8–62.3)			
May et al, 2007[32]	Third trimester, % yes	79.1 (48/61)			15.8 (21/133)
May et al, 2007[32]	Third trimester vs abstinent, OR (95% CI)	20.2 (8.9–46.6)			
May et al, 2021a[48]	First trimester, % yes	85.1 (41/48)	81.5 (53/65)	98.5 (66/67)	36.4 (43/117)
May et al, 2021a[48]	First trimester vs abstinent, OR (95% CI)	6.1 (3.0, 12.6)			
May et al, 2021a[48]	Second trimester, % yes	71.7 (34/48)	55.4 (36/65)	55.2 (37/67)	15.3 (18/117)
May et al, 2021a[48]	First and Second trimester vs abstinent, OR (95% CI)	17.3 (6.6, 45.3)			
May et al, 2021a[48]	Third trimester, % yes	55.3 (27/48)	38.5 (25/65)	28.4 (19/67)	12.5 (15/117)
May et al, 2021a[48]	First, second, and third trimester vs abstinent, OR (95% CI)	19.4 (8.2, 46.0)			
Petkovic et al, 2013[45]	First trimester, % Yes (n Yes/ all)	0			2.7 (21/769)
Petkovic et al, 2013[45]	Second trimester, % Yes (n Yes/all)	0			0.8 (6/769)
Petkovic et al, 2013[45]	Third trimester, % Yes (n Yes/all)	7.3 (4/55)			0.7 (5/769)
Quantity - Drinks per drinking day					
Chambers et al, 2019[40]	First trimester, mean (SD)	-	1.7 (0.6)	3.8 (3.1)	1.9 (2.5)
Chambers et al, 2019[40]	Second trimester, mean (SD)	-	2.0 (1.0)	2.2 (.2)	1.1 (0.7)
Chambers et al, 2019[40]	Third trimester, mean (SD)	-	1.5 (0.6)	1.8 (1.1)	1.0 (0.2)
Chambers et al, 2019[40]	Third trimester-Max number of drinks/24 hours in the past 30 days, mean (SD)	2.0 (-)	2.1 (1.5)	2.9 (1.6)	2.2 (1.3)
May et al, 2017[36]	First trimester, mean (SD)	8.4 (5.4)	6.6 (4.8)	7.9 (7.1)	5.7 (3.9)
May et al, 2017[36]	Second trimester, mean (SD)	8.5 (5.7)	6.7 (5.3)	7.4 (6.3)	6.6 (4.8)
May et al, 2017[36]	Third trimester, mean (SD)	8.9 (5.5)	7.5 (6.8)	7.3 (6.6)	8.1 (5.6)
May et al, 2016b[35]	First trimester, mean (SD)	10.4 (11.3)	6.0 (4.0)	5.5 (3.5)	5.2 (3.9)
May et al, 2016b[35]	Second trimester, mean (SD)	3.1 (1.9)	2.0 (1.3)	2.3 (1.2)	2.0 (1.2)
May et al, 2016b[35]	Third trimester, mean (SD)	13.5 (14.0)	6.7 (5.3)	6.6 (3.8)	5.7 (5.6)
May et al, 2021a[48]	First trimester, mean (SD)	8.0 (6.5)	5.1 (4.2)	6.1 (4.1)	2.1 (3.9)
May et al, 2021a[49]	Second trimester, mean (SD)	6.8 (6.9)	3.1 (4.0)	3.4 (4.3)	1.0 (3.4)
May et al, 2021a[48]	Third trimester, mean (SD)	4.2 (5.3)	2.1 (3.9)	1.9 (4.0)	0.7 (2.9)
Frequency - Drinking days per week					
May et al, 2013[33]	First trimester, Mean (SD)	2.66 (1.1)	2.22 (0.9)	2.31 (0.9)	1.67 (0.5)
May et al, 2013[33]	Second trimester, Mean (SD)	2.66 (1.2)	2.22 (0.9)	2.36 (1.1)	1.63 (0.5)
May et al, 2013[33]	Third trimester, Mean (SD)	2.56 (1.1)	2.24 (1.0)	2.69 (0.9)	1.57 (0.5)
May et al, 2017[36]	First trimester, mean (SD)	2.4 (1.5)	1.8 (1.2)	1.8 (1.3)	1.5 (0.7)
May et al, 2017[36]	Second trimester, mean (SD)	2.4 (1.4)	1.8 (1.4)	1.9 (1.4)	1.7 (0.8)
May et al, 2017[36]	Third trimester, mean (SD)	2.5 (1.5)	1.7 (1.4)	2.1 (1.6)	2.0 (0.7)
May et al, 2016b[35]	First trimester, mean (SD)	2.9 (1.8)	2.0 (1.1)	2.2 (1.1)	1.8 (0.9)
May et al, 2016b[35]	Second trimester, mean (SD)	3.1 (1.9)	2.0 (1.3)	2.3 (1.2)	2.0 (1.2)
May et al, 2016b[35]	Third trimester, mean (SD)	2.9 (0.9)	3.3 (2.6)	2.5 (0.6)	2.3 (1.0)
Frequency - Drinking days (categorised daily, per week, per month)					
Chambers et al, 2019[40]	APR First trimester				
Chambers et al, 2019[40]	Every day or almost every day, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	58.3 (7/12)	9.5 (2/21)
Chambers et al, 2019[40]	1 to 2 times/wk, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	25 (7/12)	28.6 (6/21)

Author, year	Quantity, frequency, or timing	FAS	pFAS	ARND	No FASD
Chambers et al, 2019[40]	2 to 3 times/month, % Yes (n Yes/ all)	0 (0/5)	33.3 (1/3)	8.3 (7/12)	4.8 (1/21)
Chambers et al, 2019[40]	1 times/month or less, % Yes (n Yes/ all)	0 (0/5)	66.7 (2/3)	8.3 (7/12)	57.1 (12/21)
Chambers et al, 2019[40]	Second trimester				
Chambers et al, 2019[40]	Every day or almost every day, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	55.6 (5/9)	2.6 (1/38)
Chambers et al, 2019[40]	3 to 4 times/wk, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	0 (0/9)	2.6 (1/38)
Chambers et al, 2019[40]	1 to 2 times/wk, % Yes (n Yes/ all)	0 (0/5)	33.3 (1/3)	11.1 (1/9)	13.2 (5/38)
Chambers et al, 2019[40]	2 to 3 times/month, % Yes (n Yes/ all)	0 (0/5)	66.7 (2/3)	22.2 (2/9)	2.6 (1/38)
Chambers et al, 2019[40]	1 time/month or less, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	11.1 (1/9)	78.9 (30/38)
Chambers et al, 2019[40]	Third trimester				
Chambers et al, 2019[40]	Every day or almost every day, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	41.7 (5/12)	2.3 (1/43)
Chambers et al, 2019[40]	1 to 2 times/wk, % Yes (n Yes/ all)	0 (0/5)	0 (0/3)	8.3 (1/12)	9.1 (4/43)
Chambers et al, 2019[40]	2 to 3 times/month, % Yes (n Yes/ all)	0 (0/5)	25 (1/4)	16.7 (2/12)	9.1 (4/43)
Chambers et al, 2019[40]	1 time/month or less, % Yes (n Yes/all)	0 (0/5)	75 (3/4)	33.3 (4/12)	79.5 (35/43)
May et al, 2021a[48]	First trimester				
May et al, 2021a[48]	Every day or almost every day, % Yes (n Yes/ all)	12.8 (6/48)	3.9 (3/65)	1.6 (1/67)	4.8 (6/117)
May et al, 2021a[48]	1 to 2 times/wk, % Yes (n Yes/ all)	23.1 (11/48)	21.6 (14/65)	18.8 (13/67)	11.9 (14/117)
May et al, 2021a[48]	3 to 4 times/wk, % Yes (n Yes/ all)	51.3 (25/48)	64.7 (42/65)	64.1 (43/67)	57.1 (67/117)
May et al, 2021a[48]	2 to 3 times/month, % Yes (n Yes/ all)	12.8 (6/48)	7.8 (5/65)	12.5 (8/67)	9.5 (11/117)
May et al, 2021a[48]	1 time/month or less, % Yes (n Yes/ all)	0 (0/48)	2 (1/65)	3.1 (2/67)	16.7 (20/117)
May et al, 2021a[48]	Second trimester				
May et al, 2021a[48]	Every day or almost every day, % Yes (n Yes/ all)	12.9 (6/48)	2.9 (2/65)	0 (0/67)	5.9 (7/117)
May et al, 2021a[48]	1 to 2 times/wk, % Yes (n Yes/ all)	51.6 (25/48)	67.6 (44/65)	61.1 (41/67)	47.1 (55/117)
May et al, 2021a[48]	3 to 4 times/wk, % Yes (n Yes/ all)	22.6 (11/48)	14.7 (10/65)	19.4 (13/67)	17.6 (21/117)
May et al, 2021a[48]	2 to 3 times/month, % Yes (n Yes/ all)	9.7 (5/48)	14.7 (10/65)	11.1 (7/67)	5.9 (7/117)
May et al, 2021a[48]	1 time/month or less, % Yes (n Yes/ all)	3.2 (2/48)	0 (0/65)	8.3 (6/67)	23.5 (27/117)
May et al, 2021a[48]	Third trimester				
May et al, 2021a[48]	Every day or almost every day, % Yes (n Yes/ all)	12.5 (6/48)	4.3 (3/65)	0 (0/67)	10 (12/117)
May et al, 2021a[48]	1 to 2 times/wk, % Yes (n Yes/ all)	41.7 (20/48)	60.9 (40/65)	66.7 (45/67)	50 (59/117)
May et al, 2021a[48]	3 to 4 times/wk, % Yes (n Yes/ all)	25 (12/48)	17.4 (11/65)	27.8 (19/67)	20 (23/117)
May et al, 2021a[48]	2 to 3 times/month, % Yes (n Yes/all)	16.7 (8/48)	8.7 (6/65)	5.6 (4/67)	0 (0/117)
May et al, 2021a[48]	1 times/month or less, % Yes (n Yes/ all)	4.2 (2/48)	8.7 (6/65)	0 (0/67)	20 (23/117)

Author, year	Quantity, frequency, or timing	FAS	pFAS	ARND	No FASD
Binge drinking - Yes/No					
Kesmodel et al, 2019[43]	No binge drinking	1.0			
Kesmodel et al, 2019[43]	1 or 2 times per week, OR (95% CI)	1.46 (0.9 to 2.35)			
Kesmodel et al, 2019[43]	3 or 4 times per week, OR (95% CI)	2.47 (1.79 to 3.41)			
Kesmodel et al, 2019[43]	>=5 times per week, OR (95% CI)	0.8 (0.43 to 1.49)			
May et al, 2017[36]	First trimester 3+, %	72.2	53.8	92.2	31.3
May et al, 2017[36]	First trimester 5+, %	63.5	38.5	54.9	23.2
May et al, 2017[36]	Second trimester 3+, %	58.3	35.2	74.5	18.2
May et al, 2017[36]	Second trimester 5+, %	53	25.3	41.2	14.1
May et al, 2017[36]	Third trimester 3+, %	50.9	16.5	47.1	11
May et al, 2017[36]	Third trimester 5+, %	44.8	12.1	29.4	10
May et al, 2016b[35]	First trimester 3+, %	73.5	46.1	82.1	26.6
May et al, 2016b[35]	First trimester 5+, %	64.7	31.5	48.7	17.4
May et al, 2016b[35]	Second trimester 3+, %	60.3	31.5	61.5	13
May et al, 2016b[35]	Second trimester 5+, %	55.9	21.3	35.9	9.2
May et al, 2016b[35]	Third trimester 3+, %	44.1	18	38.5	5.8
May et al, 2016b[35]	Third trimester 5+, %	39.7	12.4	30.8	4.8
Other risk classification					
		ARBD—alcohol-related birth defect			No Birth Defect
O'Leary et al, 2010[47]	First trimester - Abstinent, n(%)	17 (0.9)			1793 (93.3)
O'Leary et al, 2010[47]	First trimester - Low, n(%)	12 (0.9)			1247 (94.2)
O'Leary et al, 2010[47]	First trimester - Moderate - <70g/week or binge less than weekly, n(%)	2 (0.4)			481 (94.3)
O'Leary et al, 2010[47]	First trimester - Heavy - > 70 g/week or binge 1 or more times per week, n(%)	5 (2.9)			161 (92.0)
O'Leary et al, 2010[47]	Abstinent	1.0			
	First trimester - Low, aOR (95% CI)	1.11 (0.52–2.39)			
	First trimester - Heavy - > 70 g/week or binge 1 or more times per week, aOR (95% CI)	4.57 (1.46–14.26)			
O'Leary et al, 2010[47]	Late pregnancy - Abstinent, n(%)	17 (0.9)			1793 (93.3)
O'Leary et al, 2010[47]	Late pregnancy - Low, n(%)	18 (1.0)			1686 (93.8)
O'Leary et al, 2010[47]	Late pregnancy - Moderate - <70g/week or binge less than weekly, n(%)	9 (1.8)			475 (93.1)
O'Leary et al, 2010[47]	Late pregnancy - Heavy - > 70 g/week or binge 1 or more times per week, n(%)	2 (1.9)			97 (92.4)
O'Leary et al, 2010[47]	Abstinent	1.0			
O'Leary et al, 2010[47]	Late pregnancy - Low, aOR (95% CI)	1.25 (0.63–2.48)			
O'Leary et al, 2010[47]	Late pregnancy - Moderate - <70g/week or binge less than weekly, aOR (95% CI)	2.28 (0.98–5.30)			

Abbreviations: Foetal alcohol Syndrome (FAS); Partial Foetal Alcohol Syndrome (pFAS); Alcohol-Related Neurodevelopmental Disorder (ARND); Foetal Alcohol Spectrum Disorders (FASD); Alcohol-Related Birth Defect (ARBD); Before pregnancy recognition (BPR); After Pregnancy recognition (APR)

2.4. Discussion

Our review of international prevalence studies revealed a very wide range of estimates of national prevalence of FASD, notably affected by study methodology. Large sample studies based on passive surveillance or analysis of birth registries (which assessed children aged <1 year) estimated an FASD prevalence of less than 1 per 1000 children. Active case ascertainment studies of smaller samples of school-aged children estimated much higher prevalence, although there was still a wide range (central estimates varied from 6 per 1000 to 80 per 1000). Studies varied in terms of methods such as whether assessors were aware of mothers' drinking history, and how maternal drinking history was ascertained. Studies also differed in terms of the diagnostic criteria used, and imputation method for missing data, all of which are likely to affect the resulting estimates.

Given the very different methods used to measure exposure to alcohol shown in our review, it is not appropriate to synthesise the estimates.

Our review of dose-response and drinking patterns presents a complex picture, involving differing methods, drinking measures and FASD diagnosis thresholds, again making this impossible to synthesise in any meaningful way. More drinking during any trimester seems to be related to a higher probability of an FASD diagnosis, but it is not possible to identify a threshold below which drinking can be viewed as 'safe'.

We included only studies that identified children with FASD, therefore we cannot comment on the risk of other detrimental effects of drinking alcohol during pregnancy.

3. Expert roundtable: measuring the prevalence of foetal alcohol spectrum disorder

Our review of international studies highlights not only the wide range of prevalence estimates, but the importance of methodological approaches in terms of the resulting estimates. For this reason, we convened an expert roundtable to discuss the relative strengths and weaknesses of the different approaches to measuring prevalence. Our online roundtable meeting included researchers who were involved in the two major studies of FASD prevalence in England (see Box 1 above) as well as other experts from a variety of disciplines and professions.

3.1. Roundtable participants

Academic and clinical experts

Professor Penny Cook (Associate Dean for Research and Innovation, School of Health and Society, University of Salford).

Dr Ken Courtenay (Consultant Psychiatrist in Intellectual Disability, Barnet, Enfield and Haringey Mental Health NHS Trust, Honorary Clinical Lecturer, UCL)

Dr Cheryl McQuire (Research Fellow in Public Health Evaluation, University of Bristol)

Professor Raja Mukherjee (Consultant Psychiatrist at Surrey and Borders Partnership NHS Foundation Trust and Honorary Professor at the University of Salford)

Rachael Nielsen (NHS Greater Manchester Integrated Care Partnership, project lead on the Greater Manchester alcohol exposed pregnancy programme)

Dr Abi Rose (Senior Lecturer in Psychology, Liverpool John Moore's University)

DHSC Observers

Cristina Sanchez (Policy Analyst at DHSC)

Molly Flaherty (Senior Policy Manager in the alcohol team at the Office of Health Improvement and Disparities (OHID))

Michael Conn (Programme Management Officer at DHSC)

University of York researchers

Professor Karen Bloor (PREPARE co-lead and Professor of Health Economics and Policy, University of York) (facilitator)

Dr Ana Castro Avila (Research Fellow, PREPARE team, University of York)

Veronica Dale (Research Fellow, Statistician, PREPARE team, University of York)

Professor Kate Pickett (Professor of Social Epidemiology, University of York)

3.2. Preparation for the roundtable discussions

Before meeting, we sent the participants a slide pack containing a summary of the review findings, and some general questions to consider in advance of the meeting, namely:

1. Considering methods of **measuring** the prevalence of FASD in England

    - If you applied for a grant to measure the national prevalence of FASD in England **using primary research**, what would you propose as an **ideal** study? What choices would you make?
        - Overall approach – prospective/retrospective case ascertainment, cohort studies, disease registers?
        - Target population?
        - Sampling strategies and timing – age of children?
        - Outcome measure: diagnosis methods?
        - Exposure measure: questioning mothers about their drinking?
        - Confounding variables?
    - Methodological strengths and weaknesses
    - Practical feasibility and consideration of costs

2. Considering methods of **modelling** the prevalence of FASD in England

    - If you applied for a grant to **estimate** the national prevalence of FASD in England **using a modelling approach**, what would you propose? What choices would you make?
        - What current data exists to inform a model of drinking during pregnancy and how this links to FASD prevalence?
        - Will the new planned data from the revised Infant Feeding Survey help?
        - Can we amend existing models such as the Sheffield Alcohol Policy Model?
    - Methodological strengths and weaknesses
    - Practical feasibility and consideration of costs

3.3. Summary of the roundtable discussion

A fuller description of the roundtable discussion is provided in Appendix C. Here, we summarise the main points made by the expert group.

3.3.1. Challenges to study design

The participants expressed the view that all the relevant study design possibilities have several important limitations. In particular:

Cohort studies – have a long gap between information about exposure and the outcome. Children are not suitable for assessment until around 8 years old. Secondary analysis of existing cohort studies is low cost and can provide a longitudinal picture, as children can be tested at different ages with measures (such as growth, cognitive performance, co-ordination, communication etc.), which can map to FASD diagnosis guidelines (see box 1 or McQuire et al 2019[22] for measures used in the ALSPAC cohort), but loss to follow up and the retrospective nature of existing cohort studies is an issue. In particular:

- Existing cohort studies were not designed with FASD outcomes in mind, so measures must be mapped to FASD, providing only indicative prevalence.
- Women's drinking, although questioned during pregnancy rather than retrospectively, is difficult to measure, and in a large general cohort study, the type and number of questions may be constrained, and potentially insufficient to give an accurate measure.

It is important to ensure that any future large birth cohort studies have a strong focus on alcohol during pregnancy and on developmental measures as the child grows up.

Case ascertainment studies are costly but provide more detail and more accurate assessment. Conducted now, though, these will relate to alcohol exposure from 9-10 years ago, so will not account for current levels of and trends in alcohol consumption. They are also likely to underestimate prevalence because of pre-screen criteria (which are necessary to limit research costs but may miss some children with FASD), lack of parental consent (more likely in children at higher risk, for example parents with ongoing alcohol problems), lack of Local Authority consent for looked-after children (again a population at higher risk) and reluctance of some specialist schools to participate. All of these will bias the estimates, so statistical correction for missing data is needed with multipliers based on known underreporting. This is essentially a modelling task.

Creation and analysis of datasets based on routinely collected information and data linkage from NHS and other records could in future be very useful, particularly if improvements in recording result from a recently produced NICE quality standard.[51] This approach will not provide accurate prevalence data while FASD is still so under-diagnosed.

Modelling studies – may lack credibility and can be easy to discount in terms of hierarchy of evidence, particularly if data is constrained.

It is important to consider whether the priority for decision makers is a measure of the *prevalence of alcohol-exposed pregnancies*, or a measure of *prevalence of FASD*? These are linked but different questions and may have different implications for policy interventions. To answer both would need a study of pregnant women now and their children at around eight years old, or perhaps two studies – one of pregnant women and one of eight-year-old children.

3.3.2. Questioning women about drinking during pregnancy

A firm diagnosis of FASD relies on evidence that the mother drank alcohol during her pregnancy. Whatever study design is chosen, there is a very useful body of evidence about *how best to ask women about their drinking during pregnancy*. Very few measures have been designed specifically to measure alcohol use during pregnancy. Participants (particularly Rose) advised on this:

- Women may not tell GPs or midwives or health visitors how much they are drinking for many reasons, including stigma, discrimination, shame, and embarrassment.
- Questions should be framed in a careful, sensitive, and non-judgemental way, explaining why questions are being asked.
- Questions about pre-pregnancy behaviour can indicate risks taken into the pregnancy.
- Behaviour change happens not at the point of conception, but the point of recognising the possible pregnancy, and taking a pregnancy test.
- Questions about alcohol units are not useful as they are often very poorly understood.
- Asking broad and then more specific questions is more informative – including questions about different times in the pregnancy, and about special occasions (e.g. weddings, Christmas), to help women remember in more detail.

This advice is relevant both to future research studies and clinical practice. Since the roundtable discussion, one of the participants (Rose), with colleagues, has published a survey of alcohol consumption during pregnancy and motherhood, implementing this approach.[50] In this study, around 9% of pregnant women reported drinking since knowing they were pregnant, with a median consumption of 2.3 units each week. Most of the non-pregnant mothers reported drinking alcohol (median 6.9 units each week) with over a quarter exceeding recommended guidelines. Notably, pregnant women reported lower rates of pre-pregnancy drinking (8.8 units per week for pregnant women compared with

13.7 units for mothers), which could imply a reporting bias - pregnant women may be likely to under-report consumption even when reporting pre-pregnancy drinking.

3.3.3. Study costs and value

We discussed *possible study costs,* particularly relating to an active case ascertainment study. Similar ongoing studies mentioned by the participants seem to cost around £1000 per child. The panel mentioned a suitable sample size of around 2,000 children (ten times the Greater Manchester sample). It may also be appropriate to add in service costs, as diagnosing more children than usual will identify additional need for services and support, which should be part of any study plans. The expert group believed that future cost savings would result from such support, and even if limited to those in a case ascertainment study, resulting better outcomes might recoup some of the costs of the study. Assurance of future funding for support services would also increase the likelihood of collaboration with voluntary sector organisations.

Consent to use identifiers for onward linkage would increase the future value of any study.

3.4. Overall recommendation from the expert roundtable discussion

Overall, the expert group believed that a national prevalence study could usefully inform future policy and practice. The group favoured an *active school-based case ascertainment approach* (viewed as the gold-standard despite acknowledged limitations), supplemented by statistical correction reflecting likely under-reporting, along with consent for future data linkage and follow-up to maximise the value of the study. Such a study would likely underestimate prevalence but would provide an informative low-end estimate.

4. Reflections on options for measuring FASD prevalence

4.1. Reflecting on findings from the systematic reviews

Our review of international prevalence studies revealed a very wide range of estimates of national prevalence of FASD – from less than 1 per 1000 children to more than 80 per 1000. The estimates are notably affected by study methodology, and (as discussed in the roundtable) all the study options include inherent biases. Some published studies acknowledged the biases that had impacted the estimates, others did not.

Studies based on passive surveillance or analysis of birth registries estimated FASD prevalence of less than 1 per 1000 children, but these are limited by substantial under-diagnosis and under-reporting of FASD. Case ascertainment studies of samples of school-aged children estimated much higher prevalence, although there was still a wide range (central estimates varied from 6 per 1000 to 80 per 1000), and these studies may under- or over-estimate FASD prevalence - samples tend to be small and may not be representative of the general population.

A critical bias, inherent in all study designs, appears to be the lack of reliable recording of drinking in pregnancy, and yet a firm diagnosis relies on this information.

Studies varied in terms of important indicators such as blinding assessors to mothers' drinking history, and in terms of methods for collecting maternal drinking history. Studies also differed in terms of the diagnostic criteria used, and imputation methods for missing data, which has a substantial impact on the resulting estimates.

Our review of studies of dose-response and drinking patterns revealed very different methods of measuring exposure to alcohol. More drinking during any trimester seems to be related with a higher probability of an FASD diagnosis, but it is not possible to identify a threshold above which risk is higher. An actual dose-response relationship was hard to interpret, as there was no consistent way of reporting the drinking measure.

4.2. Reflecting on the roundtable discussion

4.2.1. Reflecting on a case ascertainment study

The expert group believed that measuring prevalence could usefully inform policy and practice; therefore, favoured a nationally representative case ascertainment study. There are, however, several serious limitations which would affect even this high-quality approach to measuring prevalence. A case-ascertainment study carried out in Greater Manchester,[23]

while using a rigorous approach and a standard World Health Organisation (WHO) protocol for enrolment, nevertheless faced a number of challenges (discussed in the roundtable).

Firstly, whilst the researchers recruited three mainstream schools successfully, one mainstream school did not engage with the research and, more importantly, the team was unable to recruit a specialist school providing social, emotional and mental health (SEMH) support, despite approaching all four of such schools in the area. Three specialist schools did not engage, and one agreed to take part but withdrew after being unable to obtain consent from any parents (this was thought to be because children were already receiving specialist support and had little to gain from a formal diagnosis).[23] Children with FASD may, though, reasonably be inferred to be more likely to attend these specialist schools.

Secondly, even in mainstream schools, the study faced problems of lack of consent in high-risk groups. In the two-stage study, 220 children were invited to initial screening (physical measures), of whom six children were opted out by parents, eight were absent and three were looked after children, opted out by the local authority. Of the 50 who screened positive – based on the physical measures, parent or teacher concerns, being already acknowledged as having special educational needs (SEN), or having experience of local authority care – 12 parents declined to consent to further investigations, along with two further local authority opt-outs. In addition, the researchers were unable to contact a further ten children, so the second stage of screening included only 26 children. The lack of parental and local authority consent is problematic because these children were all higher risk, so the resulting prevalence figures are almost certainly a significant underestimate. The Greater Manchester research team went to great lengths to engage schools and parents, and it is not clear what could be done to reduce the opt-outs from higher-risk groups. Unless these problems are somehow addressed, a national study with a larger sample size would produce another biased estimate.

Statistical imputation could help to adjust any prevalence estimate, and this would be possible with a larger sample. This would ideally need new studies to provide information on the size of the bias (e.g. recruiting a random sample of children for full assessment, to assess the pre-screen bias, and obtaining information from specialist schools – which the Greater Manchester study did not achieve). This would enable assumptions to account for recruitment biases, but such assumptions could be used to estimate prevalence through statistical modelling without launching a large, national case ascertainment study.

It is important to note that, if a national case ascertainment study was undertaken, considerable new trained staff would be needed to screen the children, and services would need to be in place to support newly diagnosed children.

4.2.2. Reflecting on asking women about their drinking during pregnancy

As discussed in the roundtable, asking women about their drinking during pregnancy (either while pregnant or retrospectively) needs a detailed and sensitive approach. This is relevant for both future research and clinical practice.

The methods suggested by Rose in the roundtable, since implemented in a published online survey, revealed that 9% of pregnant women reported alcohol use since knowing they were pregnant, with a median consumption of 2.3 units a week. Although this study is not a representative sample, researchers conducted useful public engagement and careful design of the questioning methods, to avoid stigmatising maternal drinking. The lack of validated scales tailored to pregnant women and mothers meant that the researchers adapted existing scales, with feedback from public advisors. This highlights a need for development and formal validation of maternal alcohol use scales, to build on this pilot study.

4.2.3. Reflecting on research informing actions to diagnose, prevent and treat FASD

The roundtable confirmed our reading that the science around biomarkers for maternal drinking is developing, but that existing measures are still poor.

The NICE quality standard covering assessment and diagnosis of FASD in children and young people[51] should improve both diagnosis of FASD and recording of drinking during pregnancy, which, over time, should provide a more realistic estimate of prevalence of both. At present, though, both are underestimated and cannot provide a reliable measure.

Any future research to measure prevalence should be designed to inform policies aiming to reduce the rates of FASD, and to improve outcomes for children and young people with FASD. In practice, this means that research should improve public health policy to prevent drinking during pregnancy, or improve service delivery for children facing difficulties.

4.2.3.1. Informing prevention

We question whether improving the precision of a prevalence estimate would strengthen the prevention message to women – particularly given that existing guidance from the Chief Medical Officer recommends total abstinence from alcohol. From existing research, such as the systematic review evidence in section 2, we could supplement that recommendation with an approximate estimate or a range of estimates of harm – for example 'studies show that around one in twenty children suffer adverse effects from their mothers' drinking during pregnancy'. We doubt whether improving the precision of estimate in such a statement would make any meaningful difference to the target audience. Information on

the dose of alcohol and timing of exposure which causes most harm could potentially be more useful to public health, but again, given that the current guidance is to abstain completely, this would not be translated into policy. Indeed, sharing such estimates could feasibly weaken the clear, understandable current message that any drinking during pregnancy is potentially harmful.

Our roundtable discussions included ways of communicating alcohol risks to women, and whether a more effective campaign could be informed by further research on prevalence of FASD. There are two relevant public health messages. Firstly, women planning a pregnancy should be aware that they should avoid drinking. Secondly, women with an unplanned pregnancy should be advised not to panic about any alcohol consumption before they were aware that they were pregnant, but encouraged to stop drinking now, and access help to stop if they need it. Both audiences should be aware of why drinking during pregnancy is problematic, and potential effects on their future children.

It may be that further national and local investment in health promotion activities (or the diversion of existing staff and resources) to prevent drinking during pregnancy would be strengthened by evidence of value for money. If this is the case, a more convincing estimate of incidence or prevalence could potentially be useful to policymakers.

4.2.3.2. Informing treatment

In principle, improvements in the measurement of FASD prevalence, particularly if it could be used to predict future trends, could inform service planning. In practice, though, we question whether it is necessary for service providers to have a diagnosis of FASD if a child is struggling, and whether a diagnosis should be necessary to access support. How does identifying FASD as the cause of individuals' neurodevelopmental disorders change service provision, and the resulting developmental trajectory of affected children? Could a focus on diagnosed FASD even create unfair differences between children with similar symptomatology who do and do not have a confirmed drinking history? In addition, even with good measures for alcohol use in pregnancy, there will still be a social desirability bias, which limits the chance of ever getting an accurate estimate of mild-moderate drinking during pregnancy, and hence an accurate estimate of prevalence of FASD.

More relevant information could perhaps be on the prevalence of neuro-developmental delay, and evidence on the cost-effectiveness of treatment and support. For example, the St Helen's integrated neurodevelopmental pathway[52] takes a multi-agency approach to identifying and meeting needs and includes an offer of support for families, which is accessible before, during and after the pathway journey, and also when no formal diagnosis is made.

Improvements in the design of services for developmental delay could be made, and their cost-effectiveness evaluated, without first improving the precision of estimation of FASD, and it may be a more efficient allocation of scarce resources.

5. Conclusion and recommendations

5.1. Summary of findings

Our systematic review found a wide range of estimates of prevalence of FASD, affected notably by study design. In our roundtable discussion, the expert group favoured a national prevalence study through *active school-based case ascertainment* (viewed as the gold-standard despite acknowledged limitations), supplemented by statistical correction reflecting under-reporting and consent for future data linkage and follow-up to maximise the value of the study.

Such a study would be costly (the expert group estimated costs of around £1000 per child screened, plus costs of training staff to screen children and provide advice and services for those newly diagnosed). We consider that a case ascertainment study would unavoidably be a biased estimate, underestimating prevalence, and we question whether it would usefully inform policy either to prevent FASD or improve outcomes for children with FASD or other causes of developmental delay.

5.2. Our recommendation: modelling and value of information analysis

As outlined in sections 3 and 4, all the potential study designs measuring prevalence of FASD would unavoidably produce a biased estimate. Implementing any of the methods of collecting empirical data on prevalence would need to be supplemented with statistical imputation of missing data and modelling to adjust for known biases. In practice, this would mean that the range of plausible estimates of prevalence could be narrowed with a large primary study (e.g. school-based case ascertainment) but a true precise estimate would not be possible, however many resources were invested.

We recommend, therefore, that a first step should be a modelling study, estimating the likely range of prevalence from existing information. Useful existing evidence includes the Sheffield Alcohol Policy Model,[53] although this would require substantial supplementation to estimate suspected effects of FAS and FASD. At present, the model estimates numbers of children exposed to living with an adult who has alcohol dependence (using data triangulation) in England, adjusted to generate estimates for each upper-tier local authority. It is, though, a crude estimate, not designed to measure prevalence of FASD, and there is no way of estimating the number of children exposed to prenatal alcohol exposure.

We think an extension of this model could use parameters derived from the review in section 2 of this report, alongside national and regional data on women's drinking patterns, in general and in pregnancy.

Such a modelling exercise should, we believe, be supplemented with a 'value of information' (VoI) study to assess the value of improving the precision of the estimate (narrowing the likely range of prevalence) and usefully informing decisions on future research in this area.

Value of information (VoI) is an approach "to estimating the expected benefits from collecting further information of different kinds, in scientific problems based on combining one or more sources of data. VoI methods can assess the sensitivity of models to different sources of uncertainty and help to set priorities for further data collection".[54] Its use in UK health economics has focused on decision making by NICE[55] to decide when there is sufficient evidence to justify reimbursement of new pharmaceuticals.[56] This approach separates decisions about whether an intervention should be adopted on the basis of existing evidence from whether more research should be conducted to support future decisions.

Supplementing a model of alcohol use during pregnancy with VoI analysis would enable assessment not only of which model parameters contribute most to uncertainty (using sensitivity analysis) but where we would expect further data collection to be most valuable, in terms of identifying the potential impact of changes in policy and practice that might result from a more precise estimate (using VoI analysis). This approach could inform not only the potential costs and benefits of future policy interventions aiming to reduce FASD prevalence (such as information campaigns), but also the value of improving the precision of prevalence estimates (and other parameters) by further research (such as a national case ascertainment study).

Combining modelling with VoI analysis would assess what would be gained by estimating FASD prevalence – how could alternative policies generate benefit and what levers could be used? As discussed, increasing the increasing accuracy of prevalence estimates would not influence the current national policy of recommending abstinence during pregnancy, indeed any information implying that drinking during some stages of pregnancy are more or less risky could even undermine and weaken the clear, understandable current message that any drinking during pregnancy is potentially harmful.

The value of improving prevalence estimates would, therefore, depend on what follows, i.e. what services are put in place. VoI would identify research priorities focused on policy, for example, where in the clinical pathway can we best intervene? Would further research affect service planning for a cohort of children? (and in practice can this flex in response to

potentially large numbers of new diagnoses?). Would further research affect treatment interventions – in the health or education sectors, or, for example, in making EHCP decisions? What changes in population health could be achieved, at what cost, and what cost savings might be generated? Where would additional research be most valuable?

We estimate that a modelling study, supplemented with VoI, could be achieved in around a year, costing between £250,000 and £500,000. This would provide useful information on the value of investing further in measuring the prevalence of FASD.

Appendices

Appendix A: search strategies

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 02, 2022>

1	Fetal Alcohol Spectrum Disorders/
2	(alcohol* embryopath* or alcohol* related* birth defect* or alcohol* related neurodevelopmental* disorder* or arbd or arnd or fae or fasd or fetal alcohol spectrum disorder* or fetal alcohol syndrome* or fetal* alcohol* effect* or foetal* alcohol spectrum disorder* or foetal* alcohol syndrome* or foetal* alcohol* effect or prenatal* alcohol expos* or pre-natal* alcohol expos*).ti,ab,kf,kw.
3	1 or 2
4	exp Epidemiology/
5	exp Epidemiologic Studies/
6	exp Incidence/
7	exp Prevalence/
8	(Burden or epidemiolog* or frequenc* or incidence* or morbidit* or number* or occur* or percent* or prevalence* or prevalent or probability or proportion* or rate* or statistic*).ti,kf,kw.
9	(incidence* or prevalence*).ab.
10	(cause or causal).ti.
11	Binge Drinking/
12	Alcoholic Intoxication/
13	binge drinking.ti,ab,kf,kw.
14	dose response.ti,ab,kf,kw.
15	((amount* or level* or measur$ or pattern$ or quantity or frequency or timing or daily) adj4 alcohol).ti,ab,kf,kw.
16	((level* or measur$ or pattern$ or quantity or frequency or timing or daily or behavio$) adj2 drinking).ti,ab,kf,kw.
17	or/4-16
18	*Fetal Alcohol Spectrum Disorders/et
19	*Fetal Alcohol Spectrum Disorders/ep
20	3 and 17
21	18 or 19 or 20
22	21 not (exp animals/ not humans.sh.)

Embase <1974 to 2022 December 02>

1	fetal alcohol syndrome/
2	(alcohol* embryopath* or alcohol* related* birth defect* or alcohol* related neurodevelopmental* disorder* or arbd or arnd or fae or fasd or fetal alcohol spectrum disorder* or fetal alcohol syndrome* or fetal* alcohol* effect* or foetal* alcohol spectrum disorder* or foetal* alcohol syndrome* or foetal* alcohol* effect or prenatal* alcohol expos* or pre-natal* alcohol expos*).ti,ab,kf,kw.
3	1 or 2
4	Epidemiology/
5	epidemiological data/
6	epidemiological monitoring/
7	Incidence/
8	familial incidence/
9	standardized incidence ratio/
10	Prevalence/
11	prevalence ratio/
12	point prevalence/
13	period prevalence/
14	Epidemiology.de.
15	(Burden or epidemiolog* or frequenc* or incidence* or morbidit* or number* or occur* or percent* or prevalence* or prevalent or probability or proportion* or rate* or statistic*).ti,kf,kw.
16	(incidence* or prevalence*).ab.
17	(cause or causal).ti.
18	Binge Drinking/
19	Alcohol Intoxication/
20	binge drinking.ti,ab,kf,kw.
21	dose response.ti,ab,kf,kw.
22	((amount* or level* or measur$ or pattern$ or quantity or frequency or timing or daily) adj4 alcohol).ti,ab,kf,kw.
23	((level* or measur$ or pattern$ or quantity or frequency or timing or daily or behavio$) adj2 drinking).ti,ab,kf,kw.
24	or/4-23
25	*fetal alcohol syndrome/ep
26	*fetal alcohol syndrome/et
27	3 and 24
28	25 or 26 or 27
29	28 not ((exp animal/ or nonhuman/) not exp human/)

Maternity & Infant Care Database (MIDIRS) <1971 to November 08, 2022>

1	(alcohol* embryopath* or alcohol* related* birth defect* or alcohol* related neurodevelopmental* disorder* or arbd or arnd or fae or fasd or fetal alcohol spectrum disorder* or fetal alcohol syndrome* or fetal* alcohol* effect* or foetal* alcohol spectrum disorder* or foetal* alcohol syndrome* or foetal* alcohol* effect or prenatal* alcohol expos* or pre-natal* alcohol expos*).mp.
2	(Burden or epidemiolog* or frequenc* or incidence* or morbidit* or number* or occur* or percent* or prevalence* or prevalent or probability or proportion* or rate* or statistic*).mp.
3	(cause or causal).ti.
4	binge drinking.mp.
5	dose response.mp.
6	((amount* or level* or measur$ or pattern$ or quantity or frequency or timing or daily) adj4 alcohol).mp.
7	((level* or measur$ or pattern$ or quantity or frequency or timing or daily or behavio$) adj2 drinking).mp.
8	or/2-7
9	1 and 8

Appendix B: Review tables – study methods

Table B1 Sampling method, and methods for collection of maternal drinking history during pregnancy

Source	Sampling method and data collection	Blinding to maternal drinking history	Method for collecting maternal drinking history
European Region			
May et al, 2006[18]	Data originate from in-school, first-grade samples from two health districts of the Lazio region. Using a random-number table, 25 schools were selected. Two tiers of screening. Tier I: Local school physician measured height, weight, and head circumference. Children below the 10th percentile, children referred by their teachers because of behavioural difficulties, and a random sample of children received tier II measurements. Tier II: assessment of (1) dysmorphology, physical growth, and development; (2) psychological development (intelligence and behaviour); and (3) maternal risk factors	Physicians, psychologists, and interviewers	Retrospective maternal interview
Elgen et al, 2007[20]	Children born and living in Hordaland County that were referred to the Paediatric Department, Haukeland University Hospital, for paediatric and neuropsychological assessment due to confirmed prenatal exposure to alcohol	No	Registered in the obstetric or social welfare records, or provided by the mother
Toutain et al, 2008[16]	A retrospective cohort of FAS/FASD infants was created using the mothers' obstetrical files kept in the database of the neonatology unit of a hospital near Paris	Not clear	Not clear
May et al, 2011[19]	Data originate from in-school, first-grade samples from 2 health districts of the Lazio region. 43 schools were randomly selected in two different waves. Two tiers of screening. Tier I: In-school measurement of height, weight, and head circumference. Children below the 10th percentile, children referred by their teachers because of behavioural difficulties, and a random sample of children received tier II measurements. Tier II: assessment of (1) dysmorphology, physical growth, and development; (2) psychological development (intelligence and behaviour); and (3) maternal risk factors	Physicians, psychologists, and interviewers	Retrospective maternal interview
Okulicz-Kozaryn et al, 2017[21]	All children with a signed consent form received a weight, height, and head circumference measurement. In parallel, parents and teachers reported on behavioural and/or learning difficulties. Children received the next round of assessments when they were below the 10th percentile for growth and/or had significant behavioural/learning problems. A random sample of controls also received a full	Not clear	Retrospective maternal interview

Source	Sampling method and data collection	Blinding to maternal drinking history	Method for collecting maternal drinking history
	assessment. Full assessment consisted of a dysmorphology assessment, a maternal interview, and an assessment of CNS functioning		
McQuire et al, 2019[22]	ALSPAC prospective population-based birth-cohort study of mothers and children expected to be born 1991-1992	Not clear	Maternal interview during pregnancy
Demiguel et al, 2021[17]	Data were extracted from the PMSI-MCO database for the 2006–2013 period, which includes data on all private and public maternity hospitals stays	Not clear	Not clear
McCarthy et al, 2021[23]	All children in three schools who had a signed consent form had an anthropometric measurement. The second assessment was performed to children who were below the 9th centile for height/weight or below the 2nd centile for head circumference, had learning or behavioural difficulties according to their parents or teachers, were currently or previously looked after, and those who had a diagnosed behavioural problem. The 2nd assessment consisted of an alcohol consumption maternal interview, dysmorphology assessment, and neurological impairment questionnaire	Not clear	Retrospective maternal interview
Region of the Americas			
Clarren et al, 2001[15]	All elementary schools in two counties in Washington State were asked to screen first graders for possible FAS. A child was screen positive if: 1) below 10th percentile for height or weight with at least one facial feature; or 2) one or more facial features and teacher concerns about their development or behaviour; or 3) reference on their file to gestational alcohol exposure. All screen-positive children were invited to “special diagnostic clinics” for final diagnosis and treatment planning	Not clear	Retrospective maternal interview
Poitra et al, 2003[10]	The FAS Screen was completed annually by school staff, teachers, social workers, and psychologists. Children with a positive screen (>20 points) were seen in a genetics/dysmorphology diagnostic clinic to confirm a diagnosis	Dysmorphology and clinical geneticist	Retrospective maternal interview
May et al, 2014[12]	All first-grade children from 32 schools. Those who consented received anthropometric measurements. A sample of random controls were selected to receive all measurements. Dysmorphology assessment for <25th percentile for weight, height or head circumference plus children referred by teachers and randomly selected controls. Cognitive and behavioural assessment for suspected cases plus children referred by teachers and randomly selected controls	Dysmorphology and clinical geneticist	Retrospective maternal interview
May et al, 2015[13]	All first-grade children from 17 schools. Anthropometric assessment for all consented children. Dysmorphology assessment for <10th percentile for weight, height or head circumference plus children referred by teachers and "healthy" randomly selected controls.	Physicians, psychologists, and interviewers	Retrospective maternal interview

Source	Sampling method and data collection	Blinding to maternal drinking history	Method for collecting maternal drinking history
	Cognitive and behavioural assessment for suspected cases plus children referred by teachers and "healthy" randomly selected controls.		
May et al, 2018[11]	Two sampling methods in the Midwest and Rocky Mountain regions: 1 All schools in specific districts. All children received anthropometric assessments plus dysmorphology assessment for those 25th percentile and a random sample receiving full assessment. 2 Random sample of first-grade children Different sampling method in the Pacific Southwest and Southeast region: 3 Convenience sample of schools. All children received anthropometric assessments+ Parents filled a development status report. All children <25th percentile whose parents reported developmental problems and a sample of "normal" children received dysmorphology and neuro behavioural assessments	Dysmorphology and clinical geneticist	Retrospective maternal interview
Popova et al, 2019[9]	All children attending public schools in the Greater Toronto Area were eligible. Anthropometric measurements, dysmorphology assessment and history of learning/behavioural problems for all children with a signed consent form. Children with a positive screen, received 1) a neurodevelopmental assessment; 2) maternal interview; and 3) behavioural observations/ratings by parents/guardians via the Child Behaviour Checklist (CBCL). Maternal interview for children more than two domains affected (more than 2 SD below mean). A random sample of children who completed phase I and did not have any deficits was selected	Physicians, psychologists, and interviewers	Retrospective maternal interview
May et al, 2021b[14]	Random sample from 16 public schools. Al children with a signed consent form received an anthropometric and dysmorphology assessment. Initial plan was to assess all children, but due to budgetary limitations, 84 children received the full assessment, comprising a maternal interview and neuro behavioural assessments	Dysmorphologist, and anthropometric assessors	Retrospective maternal interview
Palmeter et al, 2021[7]	National sample of Canadians aged 1 to 17 years, as of 31 January 2019, living in private dwellings in the ten provinces and three territories	Not clear	Not clear
Pei et al, 2021[8]	National dataset of children between 4 and 6 years old. Teachers complete assessment in the second half of the school year	Not clear	Not clear
Western Pacific Region			
Harris et al, 2003[25]	A retrospective chart review to identify specific ICD codes. Records of children, not recognized as having FAS but having the related codes were examined to determine whether any of these children might have FAS or related conditions. The maternal history was examined to confirm alcohol intake or alcohol related illness, if this was not apparent from the child's record. The medical records of siblings of known FAS cases were also reviewed, as these are children known to be at high risk for FAS.	No	Confirmed exposure when mother had heavy alcohol intake in either the child or maternal file, or to have had admissions related to

Source	Sampling method and data collection	Blinding to maternal drinking history	Method for collecting maternal drinking history
			intoxication, or other alcohol related illnesses.
Elliott et al, 2008[24]	Paediatricians were asked to report any cases of FAS diagnosed in a child aged <15 years. Before the study, paediatricians were given written information about the diagnostic criteria for FAS. Paediatricians were sent a pictorial lip-philtrum guide illustrating the facial abnormalities and describing how to measure palpebral fissure length	No	Retrospective maternal interview
Mutch et al, 2015[26]	Notified cases of FASD born 1980–2010 in Western Australia (WA) were identified from the WARDA, which is a register of birth defects diagnosed before 6 years of age	Not clear	Not clear

Table B2 Sampling method and diagnostic criteria used in the included studies in the dose-response review

Author	Sampling method	Diagnostic Criteria
African region		
May et al, 2007[32]	Data from 12 public schools in the West Cape Province area. Six schools were rural and six urban. Two-tier assessment: Tier I: In-school measurement of height, weight, and head circumference. Children below the 10th percentile, and a random sample of children received tier II measurements. Tier II: assessment of (1) dysmorphology; (2) psychological development (intelligence and behaviour); and (3) maternal risk factors	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD
May et al, 2013[33]	In-school measurement of height, weight, and head circumference. Children below the 25th percentile, and a random sample of children received dysmorphology and developmental assessments.	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD
May et al, 2016a[34]	Data from 53 primary schools in four small towns in the West Cape Province. Three tiers of screening. Tier I: In-school measurement of height, weight, and head circumference. Children below the 25th percentile, and a random sample of children received tier II measurements. Tier II: assessment of dysmorphology. Tier III: (1) psychological development (intelligence and behaviour) plus behavioural assessment by teacher; and (2) maternal risk factors	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD
May et al, 2016b[35]	Data from 13 primary schools in a South African community. Three tiers of screening. Tier I: In-school measurement of height, weight, and head circumference. Children below the 25th percentile, and a random sample of children received tier II measurements. Tier II: assessment of dysmorphology. Tier III: (1) psychological development (intelligence and behaviour) plus behavioural assessment by teacher; and (2) maternal risk factors	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD
May et al, 2017[36]	Data from 32 primary schools in three South African communities. Three tiers of screening. Tier I: In-school measurement of height, weight, and head circumference. Children below the 25th percentile, and a random sample of children received tier II measurements. Tier II: assessment of dysmorphology. Tier III: (1) psychological development (intelligence and behaviour) plus behavioural assessment by teacher; and (2) maternal risk factors	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD
Wynn et al, 2020[38]	Population cohort of pregnant women in 24 neighbourhoods recruited at 26 weeks on average, and reassessed at two weeks post-birth, 0.5 years, 1.5 years, 3 years, and 5 years later. Two stage system for assessment:	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD

Author	Sampling method	Diagnostic Criteria
	1) height, weight, and head circumference measurement + dysmorphology assessment. Children below the 10th percentile and those with a philtrum score>4 received stage 2 assessments. 2) A paediatrician took photograph so they could be assessed by a senior alcohol researcher	
May et al, 2021a[48]	Data from 13 schools in one community in the Western Cape Province of South Africa. Three tiers for assessments: Tier I: In-school measurement of height, weight, and head circumference. Children below the 25th percentile, and a random sample of children received tier II measurements. Tier II: assessment of dysmorphology. Tier III: (1) psychological development (intelligence and behaviour) plus behavioural assessment by teacher; and (2) maternal risk factors	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016
May et al, 2022a[37]	Data originate from 19 schools, first-grade samples from 2 two rural towns. Three tiers of screening. Tier I: In-school measurement of height, weight, and head circumference. Children below the 25th percentile, and a random sample of children received tier II measurements. Tier II: assessment of dysmorphology. Tier III: (1) psychological development (intelligence and behaviour); and (2) maternal risk factors	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016
May et al, 2022b[46]	Three samples from one community in one region and three cohort samples from four communities in a different region. All children received anthropometric assessments+ dysmorphology assessment for those 25th percentile+ random sample receiving full assessment	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016
European Region		
Kesmodel et al, 2019[43]	1628 mother and child pairs participated in the follow-up study conducted between 2003 and 2008. Maternal prenatal interview was conducted between 7 and 39 weeks of gestation. Children were assessed at 5 years of age	4-Digit diagnostic code
Mullaly et al, 2011[44]	All women who attended their first antenatal visit (12 weeks) at a large hospital in Dublin. Their records, with information about periconceptional alcohol consumption, were linked to their child's records up to hospital discharge	Not reported
Petkovic et al, 2013[45]	Data from 1st to 4th grade children in seven elementary and 13 district schools in the rural Northern region of Croatia. Anthropometric measurements and dysmorphology assessments were conducted by a paediatrician	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD
Region of the Americas		
Barr et al, 2001[39]	1439 babies of women who consecutively received prenatal care in two centres in Seattle. Interviews were conducted during their 5th month of pregnancy. About 500 babies were followed up, including the children of all heavy drinkers and some unexposed children. Because the 500 examined include almost all of the	(1) blind examination at birth by a dysmorphologist, (2) blind examination at 4 years of age by a dysmorphologist, (3) blind examination of photographs at 7 years of age

Author	Sampling method	Diagnostic Criteria
	heaviest drinkers from the original screening sample, it is assumed that all individuals with FASD were identified	by experienced observers, and/or (4) behavioural phenotype assessed from blind collected neurobehavioral data at birth through 7 years
Chambers et al, 2019[40]	Convenience sample of schools. All children received anthropometric assessments+ Parents filled a development status report. All children <25th percentile whose parents reported developmental problems and a sample of "normal" children received dysmorphology and neuro behavioural assessments	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016
Kvigne et al, 2008[41]	Children with the ICD-9-CM code 760.71 were identified from health records	(1) prenatal alcohol exposure or maternal history of alcohol consumption, (2) FAS diagnosed or noted as a suspected diagnosis by a physician, (3) one or more facial features characteristic of FAS, (4) growth deficiency (height or weight ≤10th percentile for age), and (5) central nervous system (CNS) impairment
May et al, 2022b[46]	Six population-based cohort samples from three different regions. All children received anthropometric assessments+ dysmorphology assessment for those 25th percentile+ random sample receiving full assessment	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD Revised cut-off values by Hoyme et al., 2016
Popova et al, 2020[42]	All children attending public schools in the Greater Toronto Area were eligible. Antropometric measurements, dysmorphology assessment and history of learning/behavioural problems for all children with a signed consent form. Children with a positive screen, received 1) a neurodevelopmental assessment; 2) maternal interview; and 3) behavioral observations/ratings by parents/guardians via the Child Behavior Checklist (CBCL). Maternal interview for children more than two domains affected (more than 2 SD below mean). A random sample of children who completed phase I and did not have any deficits was selected	FASD Canadian guidelines for diagnosis (2005)
O'Leary et al, 2010[47]	A 10% random sample of women who gave birth in Western Australia were invited three months after delivery. Data from respondents was linked to the birth information registered in a statutory, population-based, surveillance system of all births	The Revised Institute of Medicine (IOM) diagnostic guidelines for FASD

Appendix C: Summary of the roundtable discussions

Considering the amount of work already carried out (including the Greater Manchester case ascertainment study which demonstrated feasibility) the group thought that further pilot or feasibility testing would not add value and ideally a full prevalence study should be created.

Diagnostic guidance and thresholds can differ depending on whether they are aiming to diagnose for research or clinical purposes. Some proposed thresholds can reflect clinical constraints (e.g. the 2016 Canadian guidance, which balanced diagnostic sensitivity with protecting services from being overwhelmed). It is a complex area (Raja mentioned a review paper showing that 428 different conditions were associated with FASD). FASD is a diagnosis of exclusion – it requires clinicians to rule out prematurity, perinatal trauma, time on a neonatal unit and genetic abnormalities.

The NICE guidance simplifies debate around the different diagnostic criteria, but this is based on the Canadian criteria, with which not everyone agrees.

Active case ascertainment studies, because of time and cost, cannot provide a full assessment of every child in the sample. Most follow a tiered approach – screening first on dysmorphology, then providing a full assessment. This was the approach in the Greater Manchester study.

Accepting that case ascertainment studies give a low-end estimate, and are likely to underestimate total prevalence for a number of reasons, this is still informative. Correcting for missing data (using imputation methods) should be possible in a reasonably large sample.

Research studies (like the Greater Manchester study) provide assessment but not at the level of a full diagnosis. People slightly under a diagnostic threshold might meet criteria in the future. Ethically, if problems are identified in a study, including problems which don't meet the diagnostic threshold, people should be provided with information and support, and if appropriate, follow-up at a later date.

Ideally, clinical pathways should be neurodevelopmental, rather than differing for those with FASD and other conditions. In practice at present, services are focused on either autism or ADHD.

FASD is the most common single cause of intellectual disability (2-4% of the conditions causing intellectual effects) and it is preventable. Children whose needs are not met can result in substantial costs over time (for example in placements). Work in Canada and the US has demonstrated the cost-effectiveness of diagnosing FASD.

As part of a large case ascertainment study, it would be good to ask for consent from participants for later follow-up and data linkage. Dr McQuire and colleagues are working on

the idea of creating a national database for FASD, developing a registry with longer term linkage (through ONS and E-Child) but also with some retrospective elements from existing service data. The NICE quality standards should improve diagnosis of FASD which would improve prospective data collection.

Timing of case ascertainment is important. The general consensus is that children need to be at least 8 to demonstrate deficit in executive function not just IQ. Divergence between FASD children and others increases as they age. Ideally you would test at different time points, for example at age 8 and then again at age 11-13, so you can observe change and a likely trajectory, reflecting the complex nature of this condition.

Specialist populations – for example those in special needs schools and pupil referral units – are likely to have more FASD children but are harder to access in many ways.

Secondary analysis of existing cohort studies is low cost and can provide a longitudinal picture, with tests at different ages, but loss to follow up and the retrospective nature of existing cohort studies is an issue – these were not designed with FASD outcomes in mind, so measures have to be mapped to FASD, providing only indicative prevalence. Women's drinking and FASD is not the study's primary outcome, so the type of questions and the number of questions are not good enough to give an accurate measure

Prospective cohort studies are informative but there is a long gap between recruitment, with information about exposure, and the outcome. Children are not suitable for assessment until around 8 years old. Making sure that any future large birth cohort studies have a strong focus on alcohol during pregnancy and on developmental measures as the child grows up is important.

Data linkage from NHS and other records is useful but will not provide accurate prevalence data while FASD is still so under-diagnosed.

The group believe that active case ascertainment studies are costly but probably still the best available way to approach this, as it provides more detail and more accurate assessment. It can also reveal many neurodevelopmental disorders otherwise unidentified – reflecting unmet need.

If the UK government pursues an active case ascertainment study, a parallel study in Ireland may be possible – which would increase the sample size and provide a near-neighbour comparison.

Looking at existing English birth cohort studies (Millennium Cohort Study (MSC), Born in Bradford (BiB), Children Growing Up in Liverpool (C-GULL) and others) only C-GULL and the BiB studies are recruiting in pregnancy. All of the nationally representative cohorts were recruited at 9 months or alter. This means that we have to measure exposure retrospectively. Even questioning prospectively may need multiple measures to gain information about timing, duration and magnitude of exposure.

Asking women about drinking during pregnancy needs care. Ideally you'd ask about pre-pregnancy behaviour which gives you an indicator of the risks taken into pregnancy. Behaviour change happens not at the point of conception, but the point of identification and taking the pregnancy test. One of the participants described misconceptions about drinking in pregnancy based on stereotypes and health records, but women do not tell GPs or midwives or health visitors how much they are drinking for many reasons, including stigma and discrimination and shame and embarrassment, but also it needs time and a careful, sensitive, non-judgemental approach. Questions about units are not useful – they aren't understood. Asking broad and then more specific questions is more informative – including questions about different times in the pregnancy, and about special occasions, to help women remember in more detail. The way you question women is very important, and it is also crucial to explain to the women why we're asking the questions (to improve understanding and develop better support). It is critical that the questions we ask are acceptable to women and that they understand why we are asking them. A survey of alcohol use during pregnancy in 2-3,000 women is planned, which could create an open resource and could be added to by future studies using the same questioning strategy.

Building on this, we should skill up the workforce to be having those informed conversations and making women aware of the risks so they are able to make informed decisions. We do that quite confidently in other areas. Evidence and practice from smoking is not directly transferable. Drinking during pregnancy is emotive and there is concern about scaring pregnant women (for example anecdotes about women terminating otherwise wanted pregnancies). Communicating risks needs care, and a different approach for those planning pregnancy and those with unplanned pregnancies. One of the participants mentioned the Champion study training midwives to have conversations with pregnant women around the CMO abstinence guidelines.

It is important to remember that, for children in the looked after category, that alcohol history might have been lost.

Better understanding of mechanisms and epigenetics shows variation between individuals in terms of their own risk – we don't know and can't predict who is and isn't at risk – which is why the general message is abstinence. Explaining this to women is helpful rather than just telling them what to do, particularly when we live in a drinking culture with lots of marketing encouraging women to drink. Public health experts in Scotland are questioning whether abstinence is the right message for all because it might make women who are drinking heavily even more hidden.

Biomarkers for alcohol are still developing. Possibilities around the birth include bioassays of the placenta, and analysis of hair and meconium. Problems include the window of detection and the lack of a gold-standard reference for comparison. There are also biomarkers being studied in older children – this is a newer approach, but it isn't fully validated yet. There are several approaches now looking at urine samples and markers in that – and a range of epigenetic markers in children have been identified where we can look in children (or

adults), but we don't know how long they last for, whether they are identifiable or whether they are unique. Existing studies with biological samples could provide a resource for future biomarker analysis.

A combined approach could be useful, using multiple different research methods and triangulating the evidence, because there are flaws in every approach. If you have some active case ascertainment, some cohort studies, some modelling, that will give you the best understanding of what the likelihood is, because every approach is flawed.

Studies need to consider the clinical manifestation of services, how it presents in services, and how it affects people's lives. There is, for example, much higher prevalence among offenders, people in the criminal justice system. Economic analysis is really important, it would add weight to the case for prevention and for support services.

The Greater Manchester study research methods provide a pilot study and lessons for feasibility. They used the following pre-screen criteria:

- Being on the special educational needs list
- Some concern logged by schools or parents about milestones or behaviour
- Looked after children
- Children who are small for their age or have a small head circumference.

These criteria may mean that some children are not screened, but a full assessment on every child would be very costly (about one day's work for each child).

Out of that study's sample of a little over 200 children, 50 of them met one or other of those criteria, but the researchers only managed to get half of those (26) through to the screening. Some of the children most at risk were not included. Reasons included:

- Parents did not consent (more likely in some cases when alcohol was an ongoing issue)
- For looked-after children it was very difficult to get consent from the local authority
- Some schools did not agree (including all but one of the special schools approached, and even in the one that did agree no parents from that school consented)

This level of dropout is a methodological challenge and likely to result in a substantial underestimate of prevalence. Statistical correction for missing data is needed with multipliers based on known underreporting not possible in the GM study because of small numbers).

The Canada team and others framed studies as a general neurodevelopmental study rather than an FASD screening study to try to increase participation. One of the participants reported anecdotes of teachers telling parents 'don't worry about the alcohol questions, just lie if you're worried about that, but we really want you to get your child assessed'.

Modelling studies are constrained by the lack of robustness of the measures of prenatal alcohol exposure. The NICE quality standard should improve this over time as all routine antenatal care providers should be recording and asking alcohol use questions at three points during pregnancy, but there is not yet a standardised way of recording that. A first step needs to be to get these questions asked and recorded in a robust way. We also need urgently a standard code in SNOMED or elsewhere, to capture FASD as defined by the NICE quality standard.

Even with this, FASD is not being diagnosed routinely – clinicians don't feel confident diagnosing it or they are reluctant to because of the stigma or the lack of follow-on pathways. Similarly in midwife recording, practice is very variable. Some of them just don't like asking the questions or having the conversation, and again underreporting could be likely.

Are we looking for a measure of the prevalence of alcohol-exposed pregnancies, or a measure of prevalence of FASD? These are linked but different questions. To answer both would need a study of pregnant women now and their children at eight, or perhaps two studies – one of pregnant women and one of eight-year-old children.

Possible study costs – all the studies mentioned seem to cost around £1000 per child. In C-GULL this is not just for FASD tests – it includes many other measures. It may also be appropriate to add in service costs as diagnosing children will create a need for services and support. There is evidence of likely future cost savings from such support, and even just for those in a case ascertainment study, if it led to better outcomes this might recoup some of the costs of the study. It would also increase likelihood of collaboration with voluntary sector organisations. To maximise value, it would be worth asking participants for consent to use identifiers for onward linkage.

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