Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis

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Summary

Background **Fetal alcohol spectrum disorder (FASD) is related to many comorbidities because of the permanent effects of prenatal alcohol exposure on the fetus. We aimed to identify the comorbid conditions that co-occur in individuals with FASD and estimate the pooled prevalence of comorbid conditions occurring in individuals with fetal alcohol syndrome (FAS).**

Methods **We did a systematic literature search of studies reporting on the comorbidity and cause of death in individuals with FASD using multiple electronic bibliographic databases, searching for studies published up to July, 2012. We included original research published in a peer-reviewed journal in the English language. We used the following criteria for determining study quality: use of an established FASD diagnostic guideline, study setting, method of data collection, and sample size. All comorbid disease conditions were coded according to the International Classification of Diseases, tenth revision (ICD-10). To estimate the pooled prevalence of comorbid conditions found to co-occur in individuals with FAS, we did meta-analyses assuming a random-effects model.**

Findings **Of 5068 studies found, 127 met eligibility criteria for data extraction. From those studies, we identified 428 comorbid conditions co-occurring in individuals with FASD, spanning across 18 of 22 chapters of the ICD-10. The most prevalent disease conditions were within the sections of congenital malformations, deformities, and chromosomal abnormalities, and mental and behavioural disorders. 33 studies reported data for frequency in a total of 1728 participants with FAS. The five comorbid conditions with the highest pooled prevalence (between 50% and 91%) included abnormal results of function studies of peripheral nervous system and special senses, conduct disorder, receptive language disorder, chronic serous otitis media, and expressive language disorder.**

Interpretation **The high prevalence of comorbid conditions in individuals with FASD highlights the importance of assessing prenatal alcohol exposure as a substantial clinical risk factor for comorbidity. The harmful effects of alcohol on a developing fetus represent many cases of preventable disability, and thus, alcohol use during pregnancy should be recognised as a public health problem globally.**

Funding **Public Health Agency of Canada.**

Introduction

Findings from the most recent Global Burden of Disease and Injury study[1] showed that alcohol was the fifth leading contributor to disability and mortality—3·9% of global disability-adjusted life-years and 5·2% of all global deaths were attributable to alcohol in 2010. However, alcohol consumption often results in harm not only to the drinker, but also to others around the drinker. A classic example of such harm is the harm caused to the developing fetus by the consumption of alcohol during pregnancy.

Alcohol consumed by a pregnant woman interferes with normal developmental progression of the fetus resulting in CNS and physical damage that subsequently has several lifelong health consequences. This damage leads to fetal alcohol spectrum disorder (FASD; an umbrella term used to describe individuals who experience disability as a result of prenatal alcohol exposure). FASD includes fetal alcohol syndrome (FAS), partial FAS, and alcohol-related neurodevelopmental disorder.[2]

Since the first description of FAS by Jones and Smith in 1973,[3] the terminology used, as well as the diagnostic guidelines and recommendations have changed numerous times. Although the criteria for FASD diagnoses have been described thoroughly in the guidelines put forth to date,[2,4–11] the diagnosis of FASD remains challenging, and the specific assessment techniques used to make the definitive diagnosis are still debated, especially for alcohol-related neurodevelopmental disorder.

FASD affects individuals from all socioeconomic and ethnic backgrounds, and in addition to the individuals themselves, it can also greatly affect their families. In many cases, people with FASD require lifelong assistance from a wide range of services including health, community, remedial education, and many others. Hence, it is recognised that FASD has a substantial economic effect on any society. In North America, the lifetime cost for some cases of FASD has been estimated to be more than CAN$1 million.[12]

In spite of a substantial and growing body of scientific literature on prenatal alcohol exposure and FASD, epidemiological data for the prevalence of FASD from most countries, especially from low-income and middle-income countries, is largely absent.[13] In the USA, the prevalence of FAS in typical, mixed-racial, and

mixed-socioeconomic populations was estimated to be at least two-to-seven cases per 1000 people and the prevalence of FASD in populations of younger school children might be as high as 20–50 cases per 1000 children.[14] There are no national statistics on the prevalence of FASD in Canada; however, the crude prevalence in the general population has been roughly estimated to be about one-to-two cases per 1000 people for FAS[15] and about nine-to-ten cases per 1000 people for FASD.[16] It is postulated that the prevalence of FASD is at least ten times higher than the prevalence of FAS,[14,15,17,18] with alcohol-related neurodevelopmental disorder being the largest category of affected individuals; it has been estimated that there are three-to-four cases of alcohol-related neurodevelopmental disorder for every one case of FAS.[19]

In Europe, two independent studies have found that the prevalence of FASD is 23–47 cases per 1000 people in first grade students in Italy[20] and 40 cases per 1000 people in elementary school children in Croatia.[21] In some subpopulations, the prevalence of FASD is reported to be much higher than in the general population. For example, although outdated, the prevalence of FASD in northern communities of Canada[22] has been estimated to be about 20 times higher than the prevalence in the general population. Further, the prevalence of FASD in the Western Cape Province of South Africa, a region known for wine production and a high prevalence of binge drinking in women, has been reported to be 135–208 cases per 1000 people among first grade students.[23]

Additionally, in special populations such as children residing in child-care settings (eg, orphanages, foster care, and child welfare systems), the prevalence of FASD was estimated to be very high.[24] For example, the prevalence of FAS in an orphanage for children with special needs in Russia was reported to range from 427 to 680 cases per 1000 people.[25]

The relatively high prevalence of FASD, especially in some susceptible populations[12,22,24] behoves physicians and other health-care professionals to recognise this spectrum of disorders and the various clinical presentations that can be seen in individuals with FASD.[26]

The deficits expressed by individuals with FASD vary broadly in severity and type. Even though it is well documented that FASD is associated with a high number of comorbidities (defined herein as any coexisting conditions, regardless of causality), the existing comorbid conditions and their prevalence in individuals with FASD remain to be established. Therefore, using the existing epidemiological and medical literature, the current study aimed to: identify the comorbid conditions that co-occur in individuals with FASD, and estimate the pooled prevalence of comorbid conditions found to co-occur in individuals with FAS.

The objective to estimate the prevalence was limited to FAS given that FAS is the only expression of FASD in the WHO's International Classification of Diseases (ICD): in the ICD, ninth revision (ICD-9), Alcohol affecting fetus or newborn via placenta or breast milk 760·71, and in the ICD, tenth revision (ICD-10), Fetal alcohol syndrome (dysmorphic) Q86.0.[27,28]

Methods

Search strategy and selection criteria

The systematic literature review and meta-analyses were done and reported according to the standards set out in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[29]

We did a systematic literature search to locate original published studies that reported on the comorbidities and primary cause of death in individuals with diagnosed FASD. This search was done in the following electronic bibliographic databases: Ovid MEDLINE, PubMed, Embase, Web of Science (including Science Citation Index, Social Sciences Citation Index, Arts and Humanities Citation Index), PsycINFO, ERIC, Epscohost, CINAHL, Scopus, Campbell Collaboration, Cambridge Scientific Abstracts Sociological Abstracts, Social Work Abstracts, Canadian Centre on Substance Abuse Library

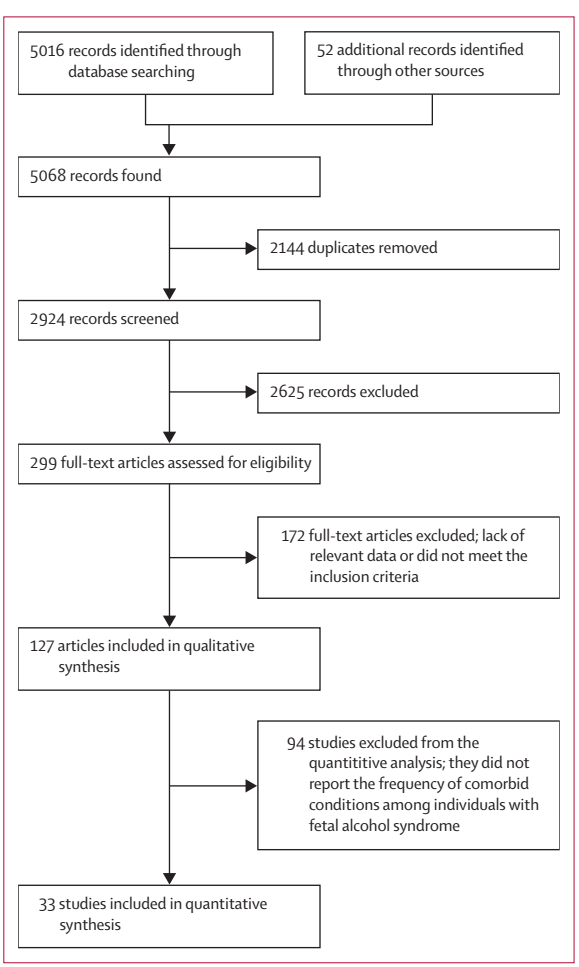

Figure 1: **Study selection**

Collection Database, and Centre for Addiction and Mental Health Library Database.

We used the following keywords: (fetal alcohol spectrum disorder* OR fetal alcohol syndrome OR partial fetal alcohol syndrome OR fetal alcohol effects OR alcohol-related neurodevelopmental disorder OR alcohol-related birth defects OR prenatal alcohol exposure) AND (death OR disabilit* OR disease* OR disorder* OR co-morbidit* OR morbidit* OR cause of death OR mortality).

Additionally to the electronic search, we manually reviewed the content pages of the major epidemiological and medical journals and the citations in the relevant articles (including all relevant review articles identified via the electronic search). The search was not limited geographically, and was done up to July, 2012, inclusively (with no restriction placed on the lower year limit).

Articles were retained if they met the following inclusion criteria: consisted of original research published in a peer-reviewed journal; were published in the English language; and reported disease conditions in individuals with diagnosed FASD or any of the diagnostic entities that fall within the FASD spectrum (ie, FAS, partial FAS, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects). Articles were excluded if they were: review articles or discussion papers, conference abstracts, or studies done on animals.

Data extraction and quality assessment

Three members of the study team independently extracted data. A fourth investigator checked table entries for accuracy against the original articles. A fifth investigator, independent of the first process, reconciled all discrepancies. The following variables were abstracted from each study: reference, country, sample size, age, and sex of participants, comorbid condition (as stated in the original paper), ICD-10 code (if available), and frequency of the comorbid condition (if available). When an article used a plain language description of the comorbid condition without stating a diagnostic code, we coded the comorbid condition using the ICD-10.

We used the following criteria for determining study quality: use of an established FASD diagnostic guideline, study setting, method of data collection, and sample size. We did not use the overall quality of the study as an exclusion criterion; rather we used the quality rating

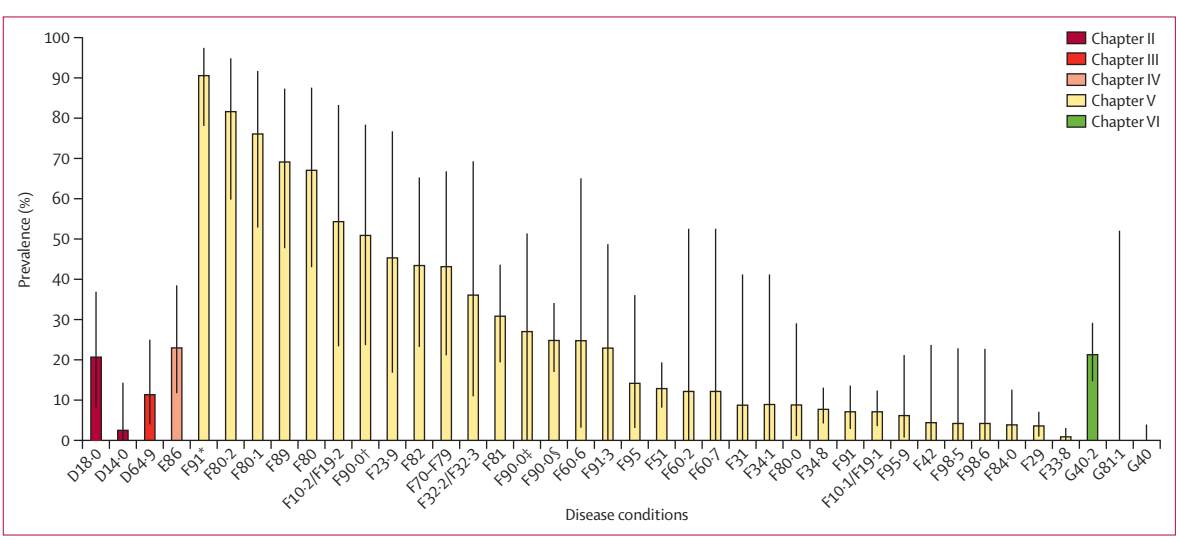

Figure 2: **Prevalence of disease conditions belonging to ICD-10 chapters II, III, IV, V, and VI found to occur in individuals with fetal alcohol syndrome**
Please note that each ICD-10 chapter is depicted by a unique colour. Each bar represents a single comorbid condition with its ICD-10 code. The height of the bar indicates the estimated pooled prevalence, and the solid vertical line within each bar represents the 95% CI for each comorbid condition. D14.0=benign neoplasm of middle ear and respiratory systems: middle ear, nasal cavity, and accessory sinuses. D18.0=haemangioma, any site. D64.9=Anaemia, unspecified. E86=volume depletion. F10.1/F19.1=mental and behavioural disorders due to use of alcohol, harmful use/mental and behavioural disorders due to use of multiple drugs and use of other psychoactive substances, harmful use. F10.2/F19.2=mental and behavioural disorders due to use of alcohol, dependence syndrome/mental and behavioural disorders due to use of multiple drugs and use of other psychoactive substances, dependence syndrome. F23.9=acute and transient psychotic disorder, unspecified. F29=unspecified nonorganic psychosis. F31=bipolar affective disorder. F32.2/F32.3=severe depressive episode without psychotic symptoms/severe depressive episode with psychotic symptoms. F33.8=other recurrent depressive disorders. F34.1=dysthymia. F34.8=other persistent mood (affective) disorders. F42=obsessive-compulsive disorder. F51=non-organic sleep disorders. F60.2=dissocial personality disorder. F60.6=anxious (avoidant) personality disorder. F60.7=dependent personality disorder. F70–F79=mental retardation. F80=specific developmental disorders of speech and language. F80.0=specific speech articulation disorder. F80.1=expressive language disorder. F80.2=receptive language disorder. F81=specific developmental disorder of scholastic skills. F82=specific developmental disorder of motor function. F84.0=childhood autism. F89=unspecified disorder of psychological development. F90.0=disturbance of activity and attention . F91=conduct disorder. F91.3=oppositional defiant disorder. F95=tic disorders. F95.8=other tic disorders. F98.5=stuttering (stammering). F98.6=cluttering. G40=epilepsy/seizure disorder. G40.2=localisation-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures. G81.1=spastic hemiplegia. Symbols are used to indicate conditions as stated in the original papers that cannot clinically and/or statistically be grouped under one code. *Conduct/behavioural problems/disruptive behaviour/impulsivity (F91.0 conducts disorders). †Attention deficit hyperactivity disorder (F90.0 disturbance of activity and attention). ‡Hyperactivity/hyperactive and inattentiveness (F90.0 disturbance of activity and attention). §Short/impaired attention span/problems/distractibility (F90.0 disturbance of activity and attention).

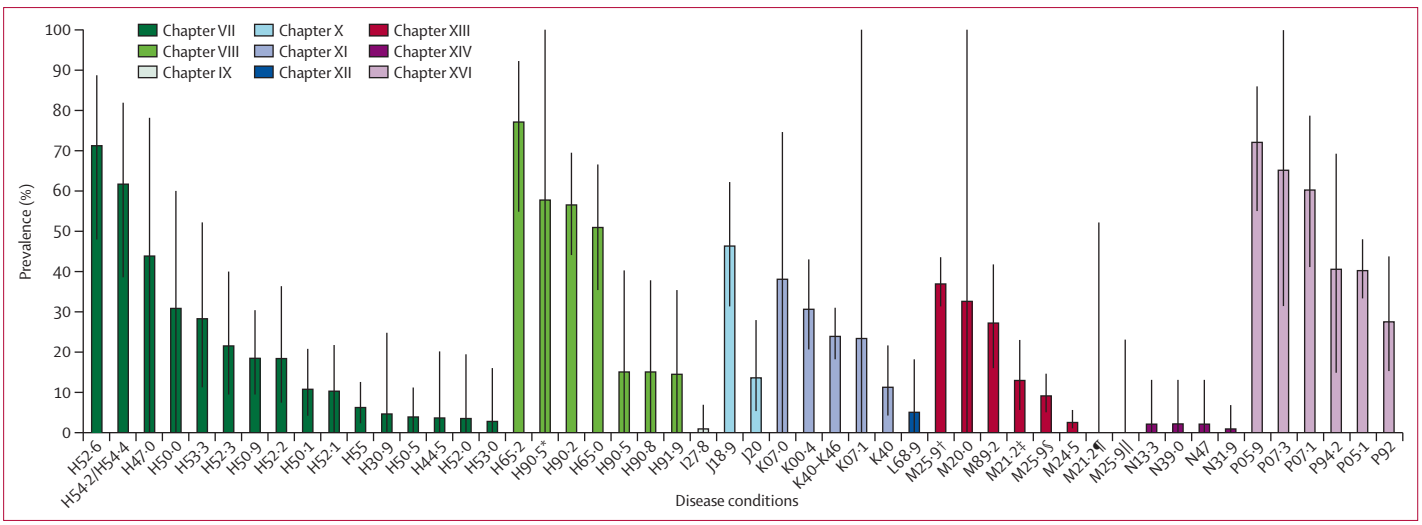

Figure 3: **Prevalence of disease conditions belonging to ICD-10 chapters VII, VIII, IX, X, XI, XII, XIII, XIV, and XVI found to occur in individuals with fetal alcohol syndrome**
Please note that each ICD-10 chapter is depicted by a unique colour. Each bar represents a single comorbid condition with its ICD-10 code. The height of the bar indicates the estimated pooled prevalence, and the solid vertical line within each bar represents the 95% CI for each comorbid condition. H30.9=chorioretinal inflammation, unspecified. H44.5=degenerated conditions of globe. H47.0=disorders of optic nerve, not elsewhere classified. H50.0=convergent concomitant strabismus. H50.1=divergent concomitant strabismus. H50.5=heterophoria. H50.9=strabismus, unspecified. H52.0=hypermetropia. H52.1=myopia. H52.2=astigmatism. H52.3=ansiometropia and aniseikonia. H52.6=other disorders of refraction. H53.0=amblyopia ex anopsia. H53.3=other disorders of binocular vision. H54.2/54.5=visual impairment including blindness (binocular or monocular). H55=nystagmus and other irregular eye movements. H65.0=acute serous otitis media. H65.2=chronic serous otitis media. H90.2=conductive hearing loss, unspecified. H90.5=sensorineural hearing loss, unspecified. H90.8=mixed conductive and sensorineural hearing loss, unspecified. H91.9=hearing loss, unspecified. I27.8=other specified pulmonary heart diseases. J18.9=pneumonia, unspecified. J20=acute bronchitis. K00.4=disturbances in tooth formation. K07.0=major anomalies of jaw size. K07.1=anomalies of jaw-cranial base relationship. K40=inguinal hernia. K40-K46=hernia. L68.9=hypertrichosis, unspecified. M20.0=deformity of finger(s). M21.2=flexion deformity. M24.5=contracture of joint. M25.9=joint disorder, unspecified. M89.2=other disorders of bone development and growth. N13.3=other and unspecified hydonephrosis. N31.9=neuromuscular dysfunction of bladder, unspecified. N39.0=urinary tract infection, site not specified. N47=redundant prepuce, phimosis and paraphimosis. P05.1=small for gestational age. P05.9=slow fetal growth, unspecified. P07.1=other low birthweight. P07.3=other preterm infants. P92=feeding problems of newborn. P94.2=congenital hypotonia. Symbols are used to indicate conditions as stated in the original papers that cannot clinically and/or statistically be grouped under one code. *Central hearing disorder (H90.5 sensorineural hearing loss, unspecified). †Incomplete extension of one or more digits (M25.9 joint disorder, unspecified). ‡Camptodactyly (M21.2 flexion deformity). §Limited joint movement/decreased pronation/supination of elbow/limited movement of knee (M25.9 joint disorder, unspecified). ¶Bilateral pes calcaneovalgus (M21.2 flexion deformity). ||Hyperextension of joints/hyperextensible joints (M25.9 joint disorder, unspecified).

(based on the study characteristics) to investigate potential sources of heterogeneity between studies, if present.

Meta-analyses of the pooled prevalence of comorbid conditions

Additionally to the described above inclusion and exclusion criteria, to estimate a pooled prevalence of the comorbid conditions found to co-occur, we included articles that reported the frequency of at least one disease condition in a cohort of individuals with FAS in the meta-analyses. We did these meta-analyses assuming that the data came from a hierarchy of different populations (ie, using a random-effects model).[30] In instances in which only one study was found for a specific disease condition, the estimate was accompanied by an exact 95% CI. To satisfy the assumption of normality when statistically combining estimates by means of meta-analyses, we transformed prevalence estimates using a double arcsine transformation so that the data followed a normal distribution.[31] We assessed heterogeneity between prevalence estimates using the Cochrane *Q*-test and the I^2 statistic.[32,33] We assessed the presence of publication bias (the possibility that studies that measured the prevalence of specific comorbidities were not published because their results differed greatly from previous estimations) using a ranked correlation test,[34] and by using a weighted regression test.[35] However, we deemed publication bias to be unlikely because an observed prevalence of FAS comorbidities that was substantially different than the previously estimated prevalence would probably have been published; therefore, we did not do an adjustment for publication bias.

We compared a subset of pooled prevalence estimates of comorbidities found to co-occur in individuals with FAS with the prevalence of the same disease conditions in the general population of the USA, obtained from the available literature.

All analyses were done using Stata version 11.0 and R version 3.0.1.

Role of the funding source

The funder had no role in the design of the study, data gathering, analysis, interpretation, or writing up the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Of 5068 studies initially found, 127 studies met inclusion criteria, and were selected for data extraction (the appendix contains the list of references). Figure 1 shows an overview of the results of the search strategy used.

See Online for appendix

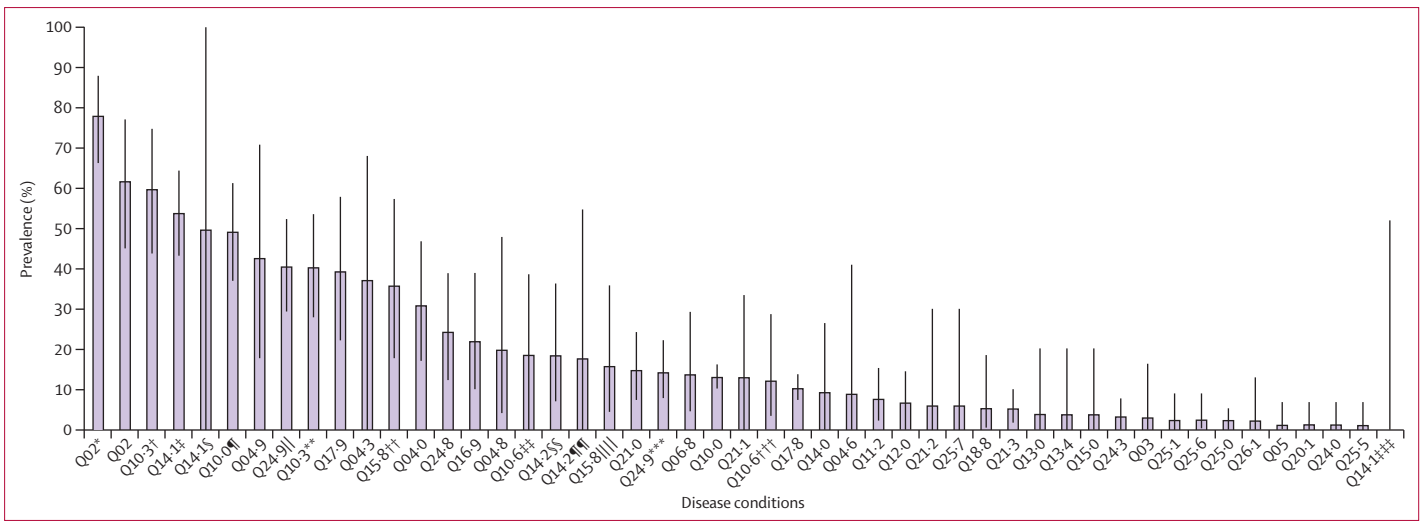

Figure 4: **Prevalence of disease conditions belonging to ICD-10 chapter XVII (Q00–Q28) found to occur in individuals with fetal alcohol syndrome**
Please note that each ICD-10 chapter is depicted by a unique colour. Each bar represents a single comorbid condition with its ICD-10 code. The height of the bar indicates the estimated pooled prevalence, and the solid vertical line within each bar represents the 95% CI for each comorbid condition. Q02=microcephaly. Q03=congenital hydrocephalus. Q04.0=congenital malformations of corpus callosum. Q04.3=other reduction deformities of brain. Q04.6=congenital cerebral cysts. Q04.8=other specified congenital malformations of brain. Q04.9=congenital malformation of brain, unspecified. Q05=spina bifida. Q06.8=other specified congenital malformations of spinal cord. Q10.0=congenital ptosis. Q10.3=other congenital malformations of eyelid. Q10.6=other congenital malformations of lacrimal apparatus Q11.2=microphthalmos. Q12.0=congenital cataract. Q13.0=coloboma of iris. Q13.4=other congenital corneal malformation. Q14.0=congenital malformation of vitreous humour. Q14.1=congenital malformation of retina. Q14.2=congenital malformation of optic disc. Q15.0=congenital glaucoma. Q15.8=other specified congenital malformations of eye. Q16.9=congenital malformation of ear causing impairment of hearing, unspecified. Q17.8=other specified congenital malformations of ear. Q17.9=congenital malformations of ear, unspecified. Q18.8=other specified congenital malformations of face and neck. Q20.1=Double outlet right ventricle. Q21.0=ventricular septal defect. Q21.1=atrial septal defect. Q21.2=atrioventricular septal defect. Q21.3=tetralogy of Fallot. Q24.0=dextrocardia. Q24.3=pulmonary infundibular stenosis. Q24.8=other specified congenital malformations of heart. Q24.9=congenital malformation of heart, unspecified). Q25.0=patent ductus arteriosus. Q25.1=coarctation of aorta. Q25.5=atresia of pulmonary artery. Q25.6=stenosis of pulmonary artery. Q25.7=other congenital malformations of pulmonary artery. Q26.1=persistent left superior vena cava. Symbols are used to indicate conditions as stated in the original papers that cannot clinically and/or statistically be grouped under one code. *Occipitofrontal/small head circumference (<10th percentile ; Q02 microcephaly). †Short/narrow palpebral fissures (Q10.3 other congenital malformations of eyelid). ‡Coccygeal fovea (Q14.1 congenital malformation of retina). §Retinal tortuosity/tortuosity of retinal vessels (Q14.1 congenital malformation of retina). ¶Blepharophimosis (Q10.0 congenital ptosis). ||Cardiac lesions (Q24.9 congenital malformation of heart, unspecified). **Epicanthal folds/broad epicanthus/prominent epicanthic folds (Q10.3 other congenital malformations of eyelid). ††Tortuosity of arteries in the eye (Q15.8 other specified congenital malformations of eye). ‡‡Short inner canthal distance (Q10.6 other congenital malformations of lacrimal apparatus). §§Small optic disc (Q14.2 congenital malformation of optic disc). ¶¶Hypoplastic optic discs/optic disc hypoplasia (Q14.2 congenital malformation of optic disc). ||||Extensive malformation of eye(s)/eye anomalies/intraocular defects (Q15.8 other specified congenital malformations of eye). ***Congenital heart disease (Q24.9 congenital malformation of heart, unspecified). †††Telecanthus (Q10.6 other congenital malformations of lacrimal apparatus). ‡‡‡Bilateral maculopathy (Q14.1 congenital malformation of retina).

Only two articles reported on cause of death data (ie, mortality data) in individuals with FASD.[36,37]

On the basis of the data reported in 127 studies, we identified 428 comorbid conditions that co-occur in individuals with FASD (appendix pp 1–13), including both medical conditions and dysmorphic features that discriminate individuals with FAS from those without. These comorbid conditions co-occurring in individuals with FASD spanned across 18 of the 22 chapters of the ICD-10. The most prevalent disease conditions were within the sections of congenital malformations, deformities, and chromosomal abnormalities (Q00-Q99; chapter XVII), and mental and behavioural disorders (F00-F99; chapter V).

33 (26%) of the 127 studies reported data on the frequency of at least one disease condition in individuals with FAS, and thus were eligible to be included in the meta-analyses.[20,22,38–68] Studies (ie, study populations) were from the following countries: Canada (six studies[22,38,51,52,61,68]), Germany (four studies[49,53,58,65]), Ireland (one study[43]), Italy (one study[20]), Norway (one study[60]), Portugal (one study[64]), Scotland (one study[59]) South Africa (three studies[50,57,66]) Sweden (three studies[48,54,55]), and USA (12 studies[39–42,44–47,56,62,63,67]).

The studies used different classifications or terms of FASD, which is reflective of the modifications made to the classifications or terms over the years and the different terminology used around the world. The following combinations of FASD diagnoses were observed in the examined studies: FAS, partial FAS, and alcohol-related neurodevelopmental disorder; FAS and partial FAS; partial FAS, alcohol-related neurodevelopmental disorder, and fetal alcohol effects; FAS and fetal alcohol effects; FAS and prenatal alcohol exposure; and alcohol embryopathy.

The studies included in the meta-analyses used the following diagnostic guidelines: Hoyme clarification of the Institute of Medicine (IOM) diagnostic criteria[8] (five studies[20,46,48,50,57]); the diagnostic guidelines by Sokol and Clarren[9] (four studies[53,54,56,64]); the criteria put forth by the Fetal Alcohol Study Group of the Research Society on Alcoholism[11] (two studies[22,40]); the guidelines by Majewski[69,70] (two studies[58,65]); the IOM diagnostic criteria[10] (one study[66]); the Centre for Disease Control FAS diagnostic guidelines[5] (one study[60]); the FASD Diagnostic Checklist[71] (one study[39]); the Canadian Guidelines[2] (one study[38]); the guidelines by Clarren and Smith[7] (one study[43]); and the

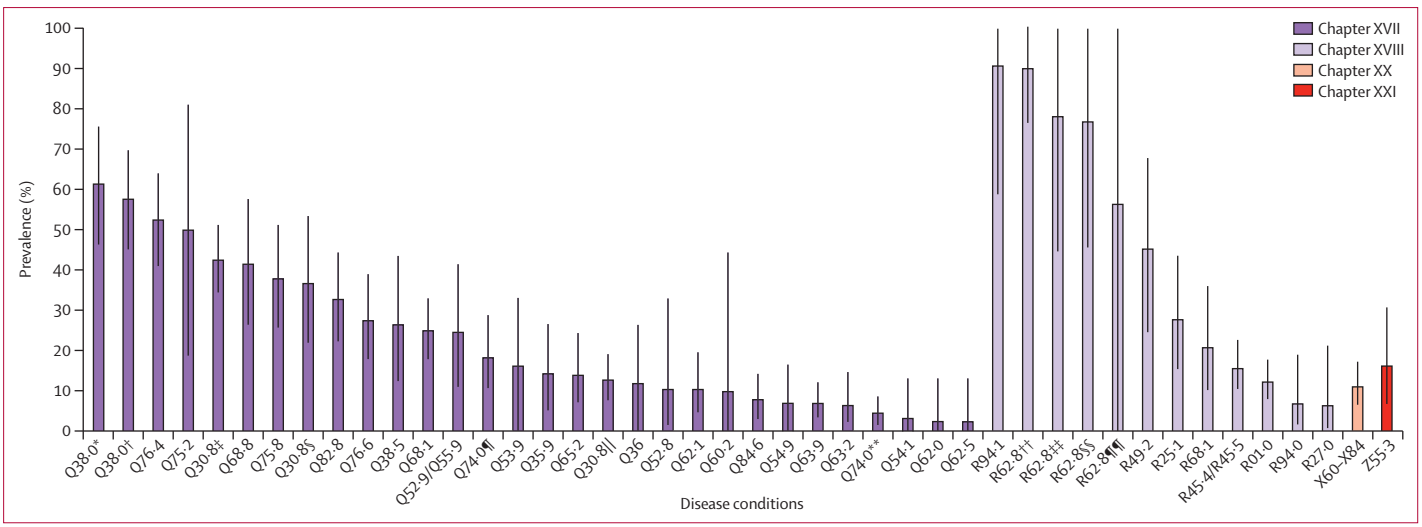

Figure 5: **Prevalence of disease conditions belonging to ICD-10 chapters XVII (Q30-Q99), XVIII, XX, and XXI found to occur in individuals with fetal alcohol syndrome**
Please note that each ICD-10 chapter is depicted by a unique colour. Each bar represents a single comorbid condition with its ICD-10 code. The height of the bar indicates the estimated pooled prevalence, and the solid vertical line within each bar represents the 95% CI for each comorbid condition. Q30.8=other congenital malformations of nose. Q35.9=cleft palate, unspecified. Q36=cleft lip. Q38.0=congenital malformations of lip, not elsewhere classified. Q38.5=congenital malformations of palate, not elsewhere classified. Q52.8=other specified congenital malformations of female genitalia. Q52.9/Q55.9=congenital malformation of female genitalia, unspecified/congenital malformation of male genital organ, unspecified. Q53.9=undescended testicle, unspecified. Q54.1=hypospadias, penile. Q54.9=hypospadias, unspecified. Q60.2=renal agenesis, unspecified. Q62.0=congenital hydronephrosis. Q62.1=atresia and stenosis of ureter. Q62.5=duplication of ureter. Q63.2=ectopic kidney. Q63.9=congenital malformation of kidney, unspecified. Q65. 2=congenital dislocation of hip, unspecified. Q68.1=congenital deformity of hand. Q68.8=other specified congenital musculoskeletal deformities. Q74.0=other congential malformations of upper limb(s), including shoulder girdle. Q75.2=hypertelorism. Q75.8=other specified congenital malformations of skull and face bones. Q76.4=other congenital malformations of spin, not associated with scoliosis. Q76.6=other congenital malformations of ribs. Q82.8=other specified congenital malformations of skin. Q84.6=other congenital malformations of nails. R01.0=benign and innocent cardiac murmurs. R25.1=tremor, unspecified. R27.0=ataxia, unspecified. R45.4/R45.5=irritability and anger/hostility. R49.2=hypernasality and hyponasality. R62.8=other lack of expected normal physiological development. R68.1=nonspecific symptoms peculiar to infancy. R94.0=abnormal results of function studies of CNS. R94.1=abnormal results of function studies of peripheral nervous system and special senses. X60-X84=intentional self-harm. Z55.3=underachievement in school. Symbols are used to indicate conditions as stated in the original papers that cannot clinically and/or statistically be grouped under one code.*Narrow vermilion border/thin upper lip (Q38.0 congenital malformations of lip, not elsewhere classified). †Long/smooth/indistinct/poorly developed philtrum (Q38.0 congenital malformations of lip, not elsewhere classified). ‡Flat/low/broad/deep nasal bridge (Q30.8 other congenital malformations of nose). §Short/small upturned nose (Q30.8 other congenital malformations of nose). ¶Hypoplastic radial head (Q74.0 other congential malformations of upper limb(s), including shoulder girdle). ||Anteverted nares/nostrils (Q30.8 other congenital malformations of nose). **Radio-ulnar synostosis/deformity/terminal transverse defect of forearm/hand (Q74.0 other congential malformations of upper limb(s), including shoulder girdle). ††Prenatal/postnatal growth retardation/deficiency (R62.8 other lack of expected normal physiological development). ‡‡Height <10th percentile (R62.8 other lack of expected normal physiological development). §§Weight <10th percentile (R62.8 other lack of expected normal physiological development). ¶¶Failure to thrive (R62.8 other lack of expected normal physiological development).

guidelines by Sokol and Clarren[9] in combination with the criteria put forth by the Fetal Alcohol Study Group of the Research Society on Alcoholism[11] (one study[61]). Lastly, 14 studies[41,42,44,45,47,49,51,52,55,59,62,63,67,68] claimed that they used diagnostic criteria for diagnosing FAS, but the references were not stated. The appendix (pp 14–16) shows the study characteristics and quality ratings of the studies included in the meta-analyses.

These 33 studies, selected for the meta-analyses, included 1728 participants with FAS and reported frequencies for 183 comorbid conditions coded in ICD-10. Thus, to estimate a pooled prevalence for each comorbid condition found to co-occur in individuals with FAS, we undertook 183 meta-analyses. The frequencies of comorbid conditions derived from the same sample and published in iteration[47,51,52,63,68] were counted only once.

Figures 2–5 show the pooled prevalences of each comorbid condition (for which frequency data exist) by ICD-10 chapters.

Table 1 presents 18 comorbid conditions (excluding conditions that are part of the diagnostic criteria used for identifying FAS—ie, dysmorphic features) with a pooled prevalence higher than 50% in individuals with FAS. The five comorbid conditions with the highest pooled prevalence include: abnormal results of function studies of peripheral nervous system and special senses, conduct disorder, receptive language disorder, chronic serous otitis media, and expressive language disorder.

The appendix (pp 17–19) presents the pooled prevalence and 95% CI of comorbid conditions in individuals with FAS and the tests of heterogeneity. Heterogeneity (I^2 >75%; statistically significant Q statistics [ie, p≤0·1]) was present for the pooled analyses of 38 (21%) of 183 comorbid conditions that co-occur in individuals with FAS, which is probably due to study differences with respect to patient characteristics, definitions of comorbid condition used, study design, methodology, and sample size.

12 studies (36%) were done in the US population. Therefore, we compared the pooled prevalence of the comorbid conditions estimated to have prevalence higher than 50% in individuals with FAS with the prevalence of the same conditions in the general population of the USA, wherever data for the general population were available (table 2).

	Disease condition	Disorder as stated in original paper	Pooled prevalence (95% CI)
R94.1	Abnormal results of function studies of peripheral nervous system and special senses	Electrophysiological abnormalities in peripheral nerves	90·9% (58·7–99·8)
F91	Conduct disorder	Conduct, behavioural problems, disruptive behaviour, or impulsivity	90·7% (77·9–97·4)
F80.2	Receptive language disorder	Receptive language deficits	81·8% (59·7–94·8)
H65.2	Chronic serous otitis media	Chronic or recurrent (serous) otitis media	77·3% (54·6–92·2)
F80.1	Expressive language disorder	Expressive language deficit	76·2% (52·8–91·8)
H52.6	Other disorders of refraction	Refractive error(s)	71·4% (47·8–88·7)
F89	Unspecified disorder of psychological development	Developmental, cognitive disorder, delay(s), or mental deficiency	69·2% (47·7–87·3)
F80.9	Developmental disorder of speech and language, unspecified	Speech, language delay, disorder, retarded speech development, speech defects, or acquisition	67·2% (43·1–87·6)
P07.3	Other preterm infants	Pre-mature birth, born prematurely, or preterm birth	65·3% (31·4–100·0)
H54	Visual impairment including blindness (binocular or monocular)	Subnormal, decreased visual acuity, problems, or visual impairment	61·9% (38·4–81·9)
H90.5	Sensorineural hearing loss, unspecified	Central hearing loss	57·9% (0·0–100·0)
H90.2	Conductive hearing loss, unspecified	Conductive hearing loss	56·8% (43·9–69·3)
F10.2; F19.2	Mental and behavioural disorders due to use of alcohol, dependence syndrome; Mental and behavioural disorders due to use of multiple drugs and use of other psychoactive substances, dependence syndrome	Alcohol dependence or drug dependence	54·5% (23·4–83·3)
Q14.1	Congenital malformation of retina	Coccygeal fovea	54·1% (43·5–64·5)
Q76.4	Other congenital malformations of spine, not associated with scoliosis	Congenital fusion of cervical vertebrae or cervical spin fusion	52·6% (40·8–64·2)
H65.0	Acute serous otitis media	(Acute, serous, or serous-mucous) otitis media	51·2% (35·5–66·7)
F90.0	Disturbance of activity and attention	Attention deficit hyperactivity disorder	51·2% (23·6–78·4)
Q75.2	Hypertelorism	Hypertelorism	50·0% (18·7–81·3)

ICD-10=International Classification of Diseases, version 10.

Table 1: **Comorbid disorders with an estimated pooled prevalence over 50% (excluding disorders that are part of fetal alcohol syndrome diagnostic criteria) in individuals with fetal alcohol syndrome, by ICD-10 code**

	Disease condition	Prevalence		Fold change
		Among individuals with fetal alcohol syndrome	Among the US general population	
H54	Visual impairment including blindness (binocular or monocular)	61·9%	0·87% (blind) and 1·98% (low vision)[72]	31 to 71
H65.2	Chronic serous otitis media	77·3%	<1·0%[73]	77
H90.2	Conductive hearing loss, unspecified	56·8%	0·45% (moderate to severe hearing loss)[74]	126 to 129
H90.5	Sensorineural hearing loss, unspecified	57·9%	0·45% (moderate to severe hearing loss)[74]	126 to 129
F10.2	Mental and behavioural disorders due to use of alcohol, dependence syndrome	54·5%	12·5% (lifetime alcohol dependence)[75]	4
F19.2	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substance, dependence syndrome	54·5%	2·6% (lifetime drug dependence)[76]	21
F80.1	Expressive language disorders	76·2%	7·4% (specific language impairments)[77]	10
F80.2	Receptive language disorders	81·8%	7·4% (specific language impairments)[77]	11
F89	Unspecified disorder of psychological development	69·2%	0·71% (intellectual disabilities)[74]	97
F90	Disturbance of activity and attention	51·2%	6·7% (attention deficit hyperactivity disorder)[74]	8
F91	Conduct disorder	90·7%	9·5%[78]	10
P07.3	Other preterm infants	65·3%	11·7%[79]	6

ICD-10=International Classification of Diseases, version 10.

Table 2: **Comparison of the pooled prevalence of comorbid disorders found in individuals with fetal alcohol syndrome versus the general population of the USA, by ICD-10 code**

The pooled prevalence of the comorbid conditions found to co-occur in individuals with FAS was notably higher than in the general population (table 2).[72–79] For example, the pooled prevalence of sensorineural hearing loss, unspecified (H90.5) and conductive hearing loss, unspecified (H90.2) was estimated to be up to 129 times higher in individuals with FAS than the prevalence of moderate to severe hearing loss in the general population of the USA.[74] The pooled prevalence of unspecified disorder of psychological development (F89) was estimated to be 97 times higher in individuals with FAS than the prevalence of intellectual disabilities in the general population of the USA.[74] Further, individuals with FAS have a prevalence of visual impairment including blindness (binocular or monocular; H54) that is 31 times higher than the prevalence of low vision and 71 times higher than the prevalence of blindness in the general US population.[72]

Discussion

FASD, as indicated by the sheer number of conditions found to co-occur in this population, is a multifaceted spectrum of disorders, affecting multiple organs and systems. Human and animal data show that prenatal alcohol exposure is highly teratogenic and can alter growth and normal development in most organs and tissues in the embryo and fetus through various well described mechanisms.[80] However, it must be acknowledged that the mere occurrence of FASD with any one of these disease conditions does not necessarily represent causality.[81] Specifically, since FASD is common, other common disorders will co-occur simply because of its high prevalence. However, the findings of this study clearly demonstrate that individuals with FASD experience some comorbid disorders at rates notably higher (in some cases more than a hundred times higher) than the prevalence in the general population of the USA.

Not surprisingly, FASD is associated with staggering costs, especially to the health-care system as reported from several different countries; for example, Canada,[82–84] South Africa,[85] and the USA.[86] Yet, the costs are underestimated given that FASD is largely underdiagnosed worldwide because of limited capacity and expertise, and the need for a multidisciplinary team-based approach in diagnostic evaluation.[2] For example, a Canadian survey of all FASD multidisciplinary diagnostic clinics revealed that a 17-fold increase in diagnostic capacity is needed across Canada to diagnose the number of FASD cases that currently exist (based on a prevalence of 1%).[87]

Understandably, the number of comorbid disorders found to co-occur in individuals with FASD can also account for the lower than expected prevalence estimates of FASD (ie, underdiagnosis), probably because of the shadowing that might occur by the other disease conditions. It is likely that clinicians report the condition or illness that has brought the individual in to seek medical attention, rather than necessarily taking into consideration the potential associations and underlying causes of the condition or illness (in this case, prenatal alcohol exposure).

Thus, it is hoped that the unveiling of the wide range of comorbid conditions that co-occur in individuals with FASD will promote the routine investigation into whether or not prenatal alcohol exposure occurred in a patient with any number of the identified comorbid conditions, thereby improving screening and diagnosis. Improving screening and diagnosis would promote access to interventions and resources that might subsequently reduce the occurrence of numerous "secondary disabilities", such as mental health problems, substance misuse, inappropriate sexual behaviour, disrupted school experience, trouble with the law, and unemployment, just to list a few.[88]

The harmful effects of alcohol on a fetus, representing many cases of preventable disability, should be recognised globally as a large public health problem. The results of the present study clearly demonstrate the need for such recognition. The number of comorbidities identified to co-occur in individuals with FASD will not only raise awareness of FASD in general, but also will raise awareness of the severe consequences of prenatal alcohol exposure and, hopefully, will prevent subsequent alcohol-exposed pregnancies. This list of comorbidities will add to the armamentarium used by clinicians, especially those clinicians working with individuals who are at greater risk to be prenatally exposed to alcohol.

To our knowledge, this study is the first study to present a comprehensive list of the comorbid conditions (coded using the ICD-10) that co-occur in individuals with FASD and the pooled prevalence of comorbid conditions in individuals with FAS. However, there are several limitations that must be acknowledged. First, some studies had small samples from a clinical population or included individuals from only one ethnic population, and are thus, limited in their generalisability. Second, all efforts were made to include data from individuals with a diagnosed FASD only and exclude individuals with prenatal alcohol exposure, without a specific diagnosis of an alcohol-related disorder; however, in some cases it was not possible to separate the data. Third, the studies used different diagnostic systems, which can affect the categorisation of the diagnostic entities of FASD.

It is imperative that prevention efforts be put in place to reduce the occurrence of alcohol consumption during pregnancy. The prevalence findings of the current study highlight that there is an urgent need to establish universal screening for prenatal alcohol exposure, using a standard screening protocol, for all newborn babies, especially among at-risk populations. Such screening could: (1) lead to close monitoring of a child's development, which could in turn, facilitate early diagnosis, and the implementation of timely interventions, if necessary; (2) prevent the occurrence of secondary disabilities later in life, such as poor academic performance, mental health problems, alcohol and drug use; and (3) provide an important

opportunity to prevent the occurrence and/or recurrence of prenatal and postnatal alcohol exposure within families and across generations.

Contributors

SP led the conception and design of the study, the development of the data collection instrument, data collection, quality assessment, data analysis, and data interpretation, and wrote and revised the manuscript; SL contributed to study design, the development of the data collection instrument, performed data collection, quality assessment and extraction, assisted in data interpretation, and wrote and revised the manuscript; KS performed the statistical analysis, assisted in data interpretation, and contributed to revising the manuscript; AM and DB performed data collection, and reviewed and revised the manuscript; AEC, RASM, and JR contributed to data interpretation and reviewed and revised the manuscript.

Declaration of interests

We declare no competing interests.

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