# Clinical presentation, diagnosis, and management of fetal alcohol spectrum disorder

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*Lancet Neurol* 2019; 18: 760–70

Published Online
May 31, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30150-4

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**Although prenatal alcohol exposure causes craniofacial anomalies, growth retardation, neurological abnormalities, cognitive impairment, and birth defects, fetal alcohol spectrum disorder is underdiagnosed. Global prevalence of fetal alcohol spectrum disorder is 0·77%, with a higher prevalence of 2–5% in Europe and North America, highlighting the need for increased diagnosis and treatment. However, diagnosis remains challenging because of the poor reliability of self-reported maternal drinking histories, an absence of sensitive biomarkers, and the infrequency of diagnostic dysmorphic facial features among individuals with fetal alcohol spectrum disorder. Different diagnostic systems and disagreements over criteria have slowed progress in the diagnosis and management of the disorder. Neuroimaging shows abnormalities in brain structure, cortical development, white matter microstructure, and functional connectivity in individuals with fetal alcohol spectrum disorder. These abnormalities modify developmental trajectories and are associated with deficits in cognition, executive function, memory, vision, hearing, motor skills, behaviour, and social adaptation. Promising trials of nutritional interventions and cognitive rehabilitation therapies are underway, with the aim of treating cognitive deficits in fetal alcohol spectrum disorders.**

## Introduction

Fetal alcohol spectrum disorder can result from prenatal alcohol exposure and comprises a range of symptoms, including minor craniofacial anomalies, growth retardation, neurological abnormalities, cognitive and behavioural impairment, and birth defects.[1] The prevalence of fetal alcohol spectrum disorder in the global population is 0·77%,[2] with variation by country and epidemiological method; the prevalence in Europe and North America is 2·0–5·0%.[3] The public health burden of fetal alcohol spectrum disorder can include lifelong physical and cognitive disability, psychiatric and medical comorbidity, diminished productivity, unemployment, homelessness, and incarceration.[4] Although fetal alcohol spectrum disorder is as common as autism spectrum disorder with a global prevalence of 0·6%,[5] fetal alcohol spectrum disorder remains underdiagnosed[6] because of social stigma, diagnostic complexity, reliance on facial features, and characteristics that overlap with those of alternative diagnoses, including attention deficit hyperactivity disorder.[7] Many individuals with fetal alcohol spectrum disorder develop subtle neurodevelopmental effects, including small deficits (<1 SD) in intelligence quotient, attention, or memory that do not prompt clinical attention on their own.[6,8] Efforts to improve diagnosis of fetal alcohol spectrum disorder include studies of traditionally undiagnosed individuals who have not been referred to clinics, such as school-based populations,[2] international studies examining high-risk populations,[9] advanced three-dimensional facial imaging for screening,[10] and neurobehavioural screening tools for school-age children that could help clinicians to identify fetal alcohol spectrum disorder via cognitive and behavioural profiles.[11]

This Review summarises advances in fetal alcohol spectrum disorder research, particularly with regards to epidemiology and clinical presentation. We discuss classifications and diagnostic systems, brain anomalies in individuals with fetal alcohol spectrum disorder, pathophysiology, and management of the disorder. Although fetal alcohol spectrum disorder is typically identified clinically during childhood, we include discussion of adult fetal alcohol spectrum disorder because the clinical manifestations persist into adulthood,[4] and adult neurologists are often unfamiliar with the disorder. Prenatal alcohol exposure often occurs with polysubstance use, further complicating neurodevelopmental outcomes. However, because prenatal alcohol exposure alone can cause fetal alcohol spectrum disorder,[12] and prenatal alcohol exposure is a greater risk to neurodevelopment than exposure to tobacco, cannabis, or methamphetamine, this Review focuses on the independent consequences of prenatal alcohol exposure on fetal alcohol spectrum disorder.

## Epidemiology

In a meta-analysis of 24 studies (1416 children), the global prevalence of fetal alcohol syndrome, the most severe form of fetal alcohol spectrum disorder, was found to be 0·15%, whereas the prevalence of all prenatal alcohol exposure-related conditions was found to be 0·77%.[3] There are large regional differences in prevalence; in South Africa, the prevalence of fetal alcohol spectrum disorder was 11·1%, whereas it was 0·01% in eastern Mediterranean countries (eg, Syria and Saudi Arabia) and 0·14% in southeast Asian countries (eg, Thailand and Indonesia),[3] where there are either cultural or legal prohibitions of alcohol. The prevalence of fetal alcohol spectrum disorder in sub-Saharan Africa is unknown, but it is believed to be high because of the high frequency of binge drinking in the region.[13] An estimated prevalence of fetal alcohol spectrum disorder of 4·7% in Italy[3] has been challenged on the basis of its regional sampling methods,[14] but the data highlight the overall problem of high rates of prenatal alcohol exposure nonetheless. The variability in prevalence

estimates of fetal alcohol syndrome and fetal alcohol spectrum disorder across studies reflects differences in epidemiological methods[14] (eg, active case ascertainment, passive record surveillance, or clinical sample extrapolation)[2] and diagnostic criteria, and differential distrubution of risk factors globally,[2,3,9] including patterns of drinking during pregnancy, maternal nutrition, and prenatal care.[13] An epidemiological study of 6639 children (mean age 6·7 years) used active surveillance across four US school districts, maternal interviews, dysmorphology exams, and neurobehavioural testing to estimate prevalence of fetal alcohol spectrum disorder in those children.[2] The prevalence of fetal alcohol spectrum disorder in these four different regions of the USA ranged from 1·1% to 5·0%, and regional distribution of diagnoses ranged from 0·0% to 0·8% (27 of 6639 children across all regions) for fetal alcohol syndrome, from 0·8% to 5·9% (104 of 6639) for partial fetal alcohol syndrome, and from 0·9% to 5·0% (91 of 6639) for alcohol-related neurodevelopmental disorder.[2] Alcohol-related neurodevelopmental disorder, which has the most inclusive criteria,[1] was the most common diagnosis, with 3·4 cases for every fetal alcohol syndrome case.[2] Among 222 children with fetal alcohol spectrum disorder, only two (<1%) had been previously diagnosed,[2] confirming that fetal alcohol spectrum disorder is often overlooked.[6,15]

The high global prevalence of fetal alcohol spectrum disorder results from widespread alcohol use, including during pregnancy. Approximately 25% of US adults[16] between the ages of 18 and 34 years binge drink (defined by the US National Institute on Alcohol Abuse and Alcoholism as five or more drinks per occasion for men and four or more drinks per occasion for women), and the risk for an alcohol-exposed pregnancy in US women aged 15–44 years was 7·3%.[17] Approximately 45% of pregnancies are unplanned,[18] and fetal alcohol exposure can occur before the pregnancy is recognised, during the days after the first missed menstrual period. At this stage, alcohol can disrupt gastrulation and neurulation, resulting in the characteristic cranial dysmorphology of fetal alcohol spectrum disorder.[12,19] Binge drinking by women of childbearing age is still a problem, despite public health efforts in a number of countries (eg, Canada, Denmark, France, and the USA).[9]

Fetal alcohol spectrum disorder is a preventable condition that can be addressed through public health efforts, including supporting timely alcohol abstinence, alcohol misuse prevention, addiction treatment, and birth control. Over four decades of animal and human research, no safe level of prenatal alcohol exposure has been established.[20] Since the 1980s, pregnant women or those trying to conceive have been advised against drinking alcohol.[21–25]

## Clinical presentation

### Craniofacial dysmorphology

Craniofacial dysmorphology in fetal alcohol spectrum disorder is most commonly characterised by short palpebral fissures, a smooth philtrum, and a thin upper lip vermilion.[1,26] Clinical recognition of craniofacial dysmorphology is important because it narrows differential diagnosis in the presence of developmental brain abnormalities, neurobehavioural deficits, or a history that suggests prenatal alcohol exposure. However, dysmorphic features (typically evaluated by dysmorphologists, geneticists, and paediatricians) are not commonly detected. Clinicians should be aware of minor physical anomalies that occur in individuals with prenatal alcohol exposure: so-called railroad-track ears, ptosis, epicanthal folds, anteverted nares, midface hypoplasia, joint contractures, camptodactyly, and altered palmar creases.[26] None of these features are diagnostic of fetal alcohol spectrum disorder, but the number of minor physical anomalies correlates with the magnitude of prenatal alcohol exposure.[1] Despite the importance of dysmorphology examination, the number of individuals with fetal alcohol spectrum disorder exceeds the capacity of specialty fetal alcohol spectrum disorder clinics.[27]

### Sensory and neuropsychological abnormalities

Prenatal alcohol exposure contributes to a variety of processing abnormalities, from basic sensory processing to cognitive processing. Brain regions and sensory neurons that are involved in odour and taste perception are affected, which can cause impaired odour identification in children with fetal alcohol spectrum disorder.[28] In adults with fetal alcohol spectrum disorder, the pleasantness of alcohol odours is proportional to the magnitude of prenatal alcohol exposure.[29] This prenatal priming for alcohol could contribute to an increased risk of alcohol use disorder in those with fetal alcohol spectrum disorder.[29]

Eye development is affected by prenatal alcohol exposure, both directly through cellular toxicity, and indirectly through alterations to the normal inductive effect of adjacent brain tissue.[30,31] Prenatal alcohol exposure can cause microphthalmia with reduced palpebral fissure length, coloboma, optic nerve hypoplasia, retinal dysplasia, retinal vascular tortuosity, convergent strabismus, and low visual acuity.[30,31] Ocular abnormalities might be asymmetrical.[30,31]

Hearing, speech, and language disorders are common in individuals with fetal alcohol spectrum disorder.[32,33] Several forms of hearing loss have been reported, including conductive, sensorineural, and central hearing loss.[32,33] Atypical auditory processing has also been reported.[34] These auditory impairments might have a pronounced effect on speech, language, reading, and writing development in individuals with fetal alcohol spectrum disorder because of comorbid neurocognitive deficits, including attention and memory problems.

Developmental delay in individuals with fetal alcohol spectrum disorder might be detectable during infancy,[35] but a single assessment is insufficient because neurobehavioural impairments manifest differently at different

ages, and assessment sensitivity also varies with age. Cognitive deficits range from profound intellectual impairment to specific impairments in attention, executive functioning, memory, visual-spatial and visual-motor abilities, and school performance (eg, reading and mathematics).[36] Cognitive deficits can be present even without the physical abnormalities of fetal alcohol spectrum disorder (eg, in alcohol-related neurodevelopmental disorder).[8] Similarly, adaptive functioning and social skills are affected, potentially reducing independent living capacity.[37] Behavioural and emotional disturbances are common and can be functionally disabling.[32,38] For example, hyperactivity, poor impulse control, aggression, and poor social skills compromise school and workplace performance and might lead to criminal justice involvement.[4] However, adverse social outcomes are difficult to attribute to fetal alcohol spectrum disorder because they can also reflect an individual's disruptive social circumstances, such as living in foster homes, violence, physical and sexual abuse, and poverty.[38]

A history of maternal alcohol use or prenatal alcohol exposure should prompt health-care providers to do a comprehensive evaluation of intelligence quotient, attention, executive functioning, memory, visual-spatial and visual-motor abilities, and mental health. Although traditional neuropsychological evaluation is time-consuming, recent efforts to develop streamlined evaluations for fetal alcohol spectrum disorder[11] might simplify this important component of diagnosis.

### Neurological deficits

A detailed history of the pregnancy, including maternal alcohol misuse, might reveal prenatal alcohol exposure, but information is often unavailable or unreliable. Neurological examination results of an individual with prenatal alcohol exposure might be non-specific, such as cranial nerve abnormalities, dysarthria, hypotonia, reflex changes, or limb and gait ataxia.[39,40] Infants who have been exposed prenatally to alcohol might have walking delays and balance and coordination problems.[39,40] A meta-analysis of 11 studies of children (≤ 18 years old)[41] showed that these deficits in gross motor functioning occur more frequently in those with moderate (two to ≥14 drinks per week) to heavy (11–28 drinks per week) prenatal alcohol exposure, a diagnosis of fetal alcohol spectrum disorder, or both, compared with children without prenatal alcohol exposure. Children with prenatal alcohol exposure have larger foot angles, increased step width, and greater gait variability than non-exposed children.[42]

A qualitative review of 24 studies[43] showed that fine motor deficits (eg, visual-motor integration problems) are common in children with fetal alcohol spectrum disorder. Fine and gross motor deficits are frequently identified in children with fetal alcohol spectrum disorder with standardised tests (eg, Bruininks-Oseretsky Test of Motor Proficiency).[41,43] Children with fetal alcohol spectrum disorder have lower fine motor composite scores and manual coordination scores, and poorer graphomotor skills (eg, handwriting and grasping) compared with healthy controls.[42]

### Neuropathological abnormalities

The diverse developmental effects of alcohol account for a range of neuropathological abnormalities. An MRI study of 72 internationally adopted children (aged 4–18 years) with fetal alcohol spectrum disorder (27 [38%] of whom had fetal alcohol syndrome) identified hypoplasia of the corpus callosum and cerebellum, vascular anomalies, gliosis, perivascular space dilation, pituitary hypoplasia, ventriculomegaly, cavum septum pellucidum, and a simplified gyral pattern.[44] Heterotopias and brainstem anomalies have also been reported in children with fetal alcohol spectrum disorder.[45] A neuropathological study[46] of 174 individuals (from fetus to 65 years) with fetal alcohol spectrum disorder or heavy prenatal alcohol exposure found hypoplasia of the corpus callosum and cerebellum, ventriculomegaly, and heterotopias, as well as microcephaly, neural tube defects, and holoprosencephaly. Of the 174 individuals, a subgroup of 65 infants who died within the first year of life included eight infants (13%) with microencephaly, five infants (8%) with posterior corpus callosum dysgenesis, and four infants (6%) with heterotopias.[46] Although these studies do not have direct comparison groups, relative comparisons can be made with an MRI study of nearly 5000 typically developing children that found heterotopias in only 24 (0·5%) of children, and partial corpus callosum agenesis in two children (0·05%).[47,48] These data highlight the increased frequency of gross structural anomalies in those who have been prenatally exposed to alcohol.

The range of neuropathological findings in fetal alcohol spectrum disorder reflects many interacting factors, including variability of alcohol timing and dose, nutrition, genetics, and comorbid substance abuse. For example, alleles of the alcohol dehydrogenase gene *ADH1B* accelerate alcohol metabolism and mitigate alcohol teratogenicity.[49] The large variability in neuropathological outcomes among those with prenatal alcohol exposure poses a challenge in defining diagnostic criteria, and necessitates that fetal alcohol disorders are defined as a spectrum, rather than a single diagnostic entity.

Although the incidence of gross structural abnormalities after prenatal alcohol exposure has increased, such abnormalities are still uncommon. Therefore, clinical MRI scanning is not indicated on the basis of prenatal alcohol exposure alone. At present, clincial MRI is not sensitive to the more subtle brain anomalies resulting from prenatal alcohol exposure that are likely to contribute to neurobehavioural dysfunction.[44,45] For example, studies with group-level MRI analyses have detected cortical thinning in bilateral precentral and post-central, inferior-frontal, posterior-temporal, parietal, and superior-occipital regions,[50] as well as left orbitofrontal thickening[51]

in children with prenatal alcohol exposure. In comparison with children with no prenatal alcohol exposure, children with prenatal alcohol exposure have regional alterations in total grey matter density and volume reductions in frontal, temporal, and parietal lobes, corpus callosum, basal ganglia, thalamus, cerebellum, and amygdala (even when the analyses were statistically corrected for differences in overall brain volume).[52] A 2-year longitudinal MRI study of children (7–15 years) with fetal alcohol spectrum disorder found altered cortical volume trajectories compared with children with no prenatal alcohol exposure.[53]

Diffusion tensor imaging in children with fetal alcohol spectrum disorder shows microstructural white matter pathology that is not apparent with clinical structural MRI (figure). White matter integrity in the cerebral peduncles is atypical in children with fetal alcohol spectrum disorder and is associated with eyeblink conditioning (a sensitive marker for prenatal alcohol exposure).[54] Task-based functional MRI shows processing deficits in children with fetal alcohol spectrum disorder, including aberrant frontal-parietal connectivity during spatial working memory[55] and abnormal parietal activity during number processing.[56] Network connectivity inefficiencies occur in children with fetal alcohol spectrum disorder,[57] and network abnormalities positively correlate with white matter microstructural integrity and with the extent of prenatal alcohol exposure.[58] In summary, the brain's communication network is functionally impaired in children with fetal alcohol spectrum disorder, but not to an extent that is apparent on clinical structural MRI.

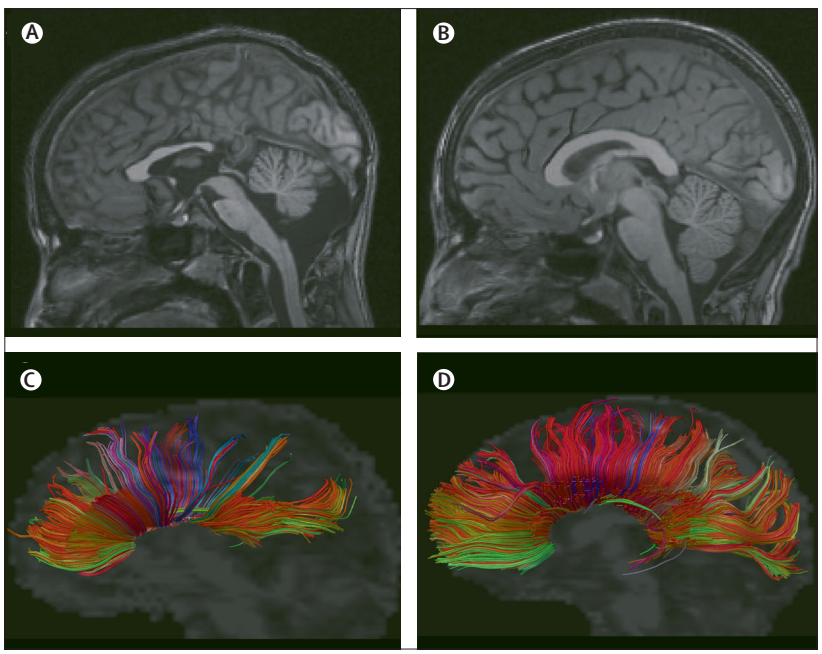


*Figure:* **MRI scans of 12-year-old boys with fetal alcohol syndrome or without prenatal alcohol exposure**
A T1-weighted anatomical image of a 12-year-old boy with fetal alcohol syndrome (A) shows multiple abnormalities, including microcephaly, partial agenesis of the corpus callosum, and cerebellar and brainstem dysplasia, which are absent in a 12-year-old boy without prenatal alcohol exposure (B). Diffusion tensor imaging tractography shows the interhemispheric white matter abnormality, especially in the posterior region, in the boy with fetal alcohol syndrome (C) compared with the boy without prenatal alcohol exposure (D).

## Diagnosis and classification

Multiple fetal alcohol spectrum disorder diagnostic and classification systems are available, each with different criteria across the four domains: magnitude of prenatal alcohol exposure, growth impairment, dysmorphic facial features, and neurodevelopmental abnormalities. Commonly used diagnostic and classification systems for fetal alcohol spectrum disorder include the fetal alcohol spectrum disorder 4-Digit Diagnostic Code,[59] the Institute of Medicine criteria revised by Hoyme and colleagues,[1] the Canadian guidelines,[60] and the Centers for Disease Control and Prevention guidelines.[61] These systems are discrepant in many respects: Hoyme and colleagues' criteria require two facial features compared with three required by other systems; the Canadian guidelines do not incorporate growth retardation as a criterion, whereas the other systems include it; the criteria from the Centers for Disease Control and Prevention are not specific regarding the extent or type of cognitive impairment, whereas other systems provide specific guidance. A study examining 1581 consecutively registered patients referred for fetal alcohol spectrum disorder evaluations[62] compared their diagnosis with use of five common diagnostic and classification systems, including the four mentioned earlier.[1,59–61] For resulting fetal alcohol spectrum disorder diagnoses (ie, fetal alcohol syndrome, partial fetal alcohol syndrome, or alcohol-related neurodevelopmental disorder), the agreement between the five systems was fair to moderate (Cohen's κ coefficient 0·24–0·58).[62] Additional work towards a universal diagnostic classification system would be beneficial.

Although each diagnostic and classification system has different advantages, in this Review we briefly describe the guidelines from the Collaboration on Fetal Alcohol Spectrum Disorder Prevalence research consortium.[2] These guidelines were based on the Institute of Medicine criteria as modified by Hoyme and colleagues,[1] and include an additional specification for the amount of alcohol exposure, as well as less stringent criteria for cognitive impairment.[2] Diagnostic criteria are separated into four fetal alcohol spectrum disorder subtypes that were originally delineated[1] by the Institute of Medicine: fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects (table).

Guidelines from the Collaboration on Fetal Alcohol Spectrum Disorder Prevalence[1] define prenatal alcohol exposure as six or more drinks per week for 2 weeks or more during pregnancy, three or more drinks per occasion at least twice during pregnancy, or documented social or legal problems related to alcohol in proximity to the index pregnancy. This threshold is lower than that for other diagnostic systems[1,59–61] and does not meet the National Institute on Alcohol Abuse and Alcoholism

| | Dysmorphic facial features | Growth deficiency | Brain abnormality | Cognitive or behavioural impairment | Other systemic malformation |
|---|---|---|---|---|---|
| **Confirmed prenatal alcohol exposure*** | | | | | |
| Fetal alcohol syndrome | Required | Required | Required | Required | Not required |
| Partial fetal alcohol syndrome | Required | Not required | Not required | Required | Not required |
| Alcohol-related neurodevelopmental disorder | Not required | Not required | Not required | Required† | Not required |
| Alcohol-related birth defect | NA | NA | NA | NA | Required |
| **No confirmed prenatal alcohol exposure** | | | | | |
| Fetal alcohol syndrome | Required | Required | Required | Required | Not required |
| Partial fetal alcohol syndrome | Required | Required if brain abnormality is not present | Required if growth deficiency is not present | Required | Not required |

NA=not applicable. *Defined as any of the following: six or more drinks per week for 2 weeks or more; three or more drinks on two or more occasions; documentation of maternal intoxication during pregnancy; positive biological test indicating that the fetus was exposed to alcohol; or evidence of risky maternal drinking on a validated screening tool (eg, WHO Alcohol Use Disorders Identification Test; maternal report includes the pregnancy itself and the 3 months before pregnancy awareness). †Alcohol-related neurodevelopmental disorder requires two behavioural or cognitive deficits if intelligence quotient is not ≥1·5 SD below the mean. For children younger than 3 years, developmental delay is required.

***Table:*** **Diagnostic criteria of fetal alcohol disorder subtypes of the Collaboration on Fetal Alcohol Spectrum Disorders Prevalence[1,2]**

threshold for binge drinking (blood alcohol concentration of 0·08 g/dL, typically occurring after four drinks for women).[63] Although fetal alcohol spectrum disorder is most readily diagnosed following higher levels of prenatal alcohol exposure attained from binge drinking, lower levels of prenatal alcohol exposure can cause subtle effects. For example, a prospective cohort study of 607 offspring of women in a prenatal clinic[64] found an association between consumption of one alcohol drink per day (in any trimester) and behavioural problems in offspring at the age of 22 years. The Growing Up in New Zealand cohort study[65] of 6156 offspring found significant differences in parent-reported infant temperament at 9 months (eg, reduced positive affect and reduced self-regulation ability), but no differences in behaviour at 2 years old, after maternal consumption of three drinks per week early in gestation.

Prenatal alcohol exposure history is not required to diagnose fetal alcohol syndrome when cardinal facial features are present because of their relative specificity. However, in the small number of patients with abnormal facial features (eg, small palpebral fissures or smooth philtrum), other causes of facial anomaly, such as genetic disorders or fetal hydantoin syndrome, should be ruled out.[26,66] According to the Collaboration on Fetal Alcohol Spectrum Disorder Prevalence criteria, fetal alcohol syndrome requires craniofacial anomalies, growth retardation, abnormal brain structure or functional impairment, such as seizure disorder, and neurobehavioural impairment (table). The Collaboration on Fetal Alcohol Spectrum Disorder Prevalence modified the revised Institute of Medicine criteria[1] by adding a requirement for neurobehavioural impairment because it contributes most to functional impairment and is the most important target for intervention. The Collaboration on Fetal Alcohol Spectrum Disorder Prevalence[2] selected a threshold of 1·5 SD below the mean for standardised measures of cognition and behaviour, which is less stringent than other diagnostic systems, some of which specify thresholds of 2·0 SD below the mean.

A diagnosis of partial fetal alcohol syndrome requires prenatal alcohol exposure history, abnormal craniofacial features, and neurobehavioural impairment (panel). Alternatively, partial fetal alcohol syndrome diagnosis can occur without a prenatal alcohol exposure history when abnormal craniofacial features, neurobehavioural impairment, and either growth deficiency or abnormal brain development are present (table). A diagnosis of alcohol-related neurodevelopmental disorder requires prenatal alcohol exposure and neurobehavioural dysfunction, but not abnormal craniofacial features or growth deficiency. Because alcohol-related neurodevelopmental disorder has the least stringent and least specific criteria, it accounts for a substantial proportion of the fetal alcohol spectrum disorder population.[2] Finally, alcohol-related birth defect is a rare diagnosis that is made when there is a prenatal alcohol exposure history and a malformation that is known to be associated with prenatal alcohol exposure (eg, affecting the cardiovascular or skeletal system).[1]

Neurobehavioural disorder associated with prenatal alcohol exposure has been proposed as a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for individuals with prenatal alcohol exposure and dysfunction in three symptom domains: neurocognition, self-regulation, and adaptive functioning.[67] Neurobehavioural disorder associated with prenatal alcohol exposure is indicated as a "condition for further study" in DSM-5,[67] in part because there is no consensus on specific thresholds for prenatal alcohol exposure (eg, a minimum level of prenatal alcohol exposure at which adverse effects are seen) or on the extent of cognitive impairment required for diagnosis. The frequency of impairments in all three symptom domains is also unknown in the population. Furthermore, adaptive functioning might be associated with confounding factors: poverty, abuse, neglect, and low socioeconomic status.[37,67] However, a direct comparison between the DSM-5 criteria[67] for neurobehavioural disorder associated with prenatal alcohol exposure and a set of alcohol-related neurodevelopmental disorder diagnostic criteria in a clinic-referred sample[68] found that the proposed criteria for neurobehavioural disorder associated with prenatal alcohol exposure correctly classified 77 (90%) of 86 individuals (with a sensitivity of 0·95 and specificity of 0·75), suggesting that these

criteria have high validity and clinical utility.[68] At present, with DSM-5, clinicians can diagnose a patient with a non-specific neurodevelopmental disorder and add "associated with prenatal alcohol exposure". In the future, the DSM might provide a more specific diagnosis for clinical use.

Social stigma about alcohol misuse, poor awareness of fetal alcohol spectrum disorder, and an inadequate capacity for diagnosis results in underdiagnosis and misdiagnosis of fetal alcohol spectrum disorder.[6,15] The high prevalence of fetal alcohol spectrum disorder and its underdiagnosis in children suggest that fetal alcohol spectrum disorder is often present but unrecognised in adults.[4,65] Cardinal facial features of fetal alcohol spectrum disorder (ie, small palpebral fissures, flattened philtrum, thin upper lip) are often evident in adulthood, although maturation causes some features to be subtle or absent.[4,69] Weight normalises during development for some individuals with fetal alcohol spectrum disorder, but short stature, microcephaly, cognitive deficits, and neurobehavioural abnormalities often persist into adulthood.[4] Diagnosing fetal alcohol spectrum disorder in children and adults is crucial for identifying comorbidities or cooccurring conditions (eg, attention-deficit hyperactivity disorder, substance abuse, or depression) and giving patients the opportunity to access vocational support, housing and financial assistance, psychological interventions, and specialised legal counselling. Access to these services can attenuate the potential effects of comorbidities, which include difficulties in getting academic qualifications or finding employment, social problems, criminal behaviour, and alcohol and drug use disorders.

### *Panel:* Case study: multidisciplinary evaluation of a child with prenatal alcohol exposure

A 7-year-old boy who had been adopted was referred to a fetal alcohol spectrum disorder clinic. The boy had been exposed to binge drinking, tobacco, and marijuana during the first trimester. His height and weight were higher than the 50th percentile (in the normal range) and head circumference was normal. He had small palpebral fissures, thin upper lip, smooth philtrum, and midface hypoplasia. Cognitive testing showed borderline intellectual functioning, with an intelligence quotient of 75, and impairments to attention, executive functioning, and fine motor skills. He had hyperactivity, aggression, and learning deficits. Based on these findings, the boy was diagnosed with partial fetal alcohol syndrome. He was not taking any medications. The boy's parents reported insomnia, frequent waking, and previous night terrors. The neurological examination was unremarkable, but an EEG showed diffuse slowing. MRI showed thinning in the posterior corpus callosum and a single focal periventricular heterotopia. The boy was given a low-dose stimulant medication and a sleep study referral. Plans were made to collect behaviour ratings from the boy's parents and teachers and to retest attention at follow-up in 1 month.

## Comorbidities

Fetal alcohol spectrum disorder is associated with neuropsychiatric and physical comorbidities. Meta-analyses of fetal alcohol spectrum disorder cohorts[32,38] show marked increases in the prevalence of a range of conditions among individuals with fetal alcohol spectrum disorder compared with population prevalence rates in the literature or published by the US National Institutes of Health.[32,38] For instance, the prevalence of behavioural disturbance is increased by eight to ten times, language disorder by ten times, intellectual impairment by 97 times, psychosis by 24 times, anxiety disorders by 11 times, otitis media by seven times, and conductive or sensorineural hearing loss by 126–129 times.[32,38] It should be acknowledged that studies based on individuals who are clinically diagnosed with fetal alcohol spectrum disorder might have inherent bias compared with population-based studies because treatment-seeking individuals might have more physical, cognitive, and behavioural problems than non-treatment-seeking individuals.[7] For example, comorbidity of attention-deficit hyperactivity disorder was found in 1523 (48%) of 3178 children with fetal alcohol spectrum disorder in a review of clinic-referred samples, compared with two (9%) of 23 in a non-referred cohort of children with fetal alcohol spectrum disorder from a school-based epidemiological study.[7]

Alternative designs can be used to complement studies of treatment-seeking individuals with fetal alcohol disorder to lessen the potential biases introduced by clinic-referred samples. One example is the prospective cohort design used in the Safe Passage study[70] of 12 000 pregnancies in South Africa and the USA, or the retrospective cohort design used in the UK Millennium Cohort Study[71] of more than 18 000 mother-child pairs. For example, the UK Millennium Cohort Study found no relationship between prenatal alcohol exposure and autism, which is an important finding given previous suggestions of overlap between the two disorders.[71,72]

A retrospective chart review[32] of 425 individuals with fetal alcohol spectrum disorder (2–49 years old) found a 5·9% prevalence of epilepsy compared with 0·5% in the general population. A prospective study[73] of 61 internationally adopted children (5–16 years old) with fetal alcohol spectrum disorder reported seizures or abnormal EEG results in 15 (25%) of the children and status epilepticus during sleep was reported in one (2%) of the children. The higher prevalence of epilepsy in the prospective study[73] compared with the retrospective review[32] could be due to the inclusion of individuals with abnormal EEG results and the high-risk population that was being studied (internationally adopted children). Although the specific mechanisms by which prenatal alcohol exposure causes epilepsy are not fully known,

malformations of cortical development, such as heterotopias or polymicrogyria, might contribute.[74] In addition, copy number variation or hypermethylation of cytosine-guanine dinucleotide sites in genes associated with neurodevelopmental disorder and epilepsy might be involved in the mechanism.[75,76]

Sleep disturbances are common comorbidities in individuals with fetal alcohol spectrum disorder and might contribute to neurobehavioural deficits.[77] Clinical assessment and polysomnography identified sleep disorders, most of which were previously undiagnosed, in 20 (58%) of 36 children and adolescents from a fetal alcohol spectrum disorder clinic,[78] as compared with 20–30% in this age range in the general population. Insomnia and parasomnias (including both rapid eye movement and non-rapid eye movement parasomnias) were observed most frequently, followed by sleep apnoea and nocturnal enuresis.[78] Additionally, diminished sleep efficiency and sleep fragmentation were seen in seven (20%) of 36 children with fetal alcohol disorder who were not diagnosed with a sleep disorder.[78] Of 24 children with a melatonin profile, 19 (79%) had anomalies, including both delayed secretion and advanced secretion patterns.[78] Sleep disturbances in children with fetal alcohol spectrum disorder can result from abnormalities in central respiratory modulation, upper airway obstruction, disruption of circadian rhythms, and damage to the suprachiasmatic nucleus and the associated sleep neural circuitry.[77] Therefore, clinicians should evaluate and manage sleep disturbances in individuals with prenatal alcohol exposure or fetal alcohol spectrum disorder.

## Pathophysiology

In both animals and humans, alcohol equilibrates freely from maternal to fetal circulation, disrupting maternal, placental, and fetal physiology.[79] In animal models, the extent of disruption is determined in part by the dose, pattern, and timing of prenatal alcohol exposure.[12] In rodents, alcohol exposure during gastrulation (approximately equivalent to day 17 of human gestation) can result in the cardinal craniofacial features of fetal alcohol syndrome, such as small palpebral fissures and abnormalities in the upper lip and philtrum area. Exposure during neurulation (approximately equivalent to the third and fourth weeks of human gestation) can result in facial abnormalities that are typical of DiGeorge syndrome in humans, a genetic condition with phenotypic features that are sometimes observed in fetal alcohol spectrum disorder.[12] Prenatal alcohol exposure later in gestation, after organogenesis, has a considerably reduced effect on craniofacial development, but it continues to disrupt brain development throughout gestation.[12] These animal model findings might explain why alcohol-related neurodevelopmental disorder includes marked neurocognitive and behavioural abnormalities but does not include any defining facial dysmorphology.[1]

Animal models show that the mechanisms by which prenatal alcohol exposure disrupts development include genetic, epigenetic, molecular, cellular, and physiological activities that alter the complex processes of development across the lifespan.[80] For example, alcohol metabolism produces oxidative injury as well as toxic metabolites (eg, acetaldehyde), and in animal models, antioxidants can mitigate alcohol teratogenesis.[81] Apoptotic death and impaired migration of neural crest cells leads to brain and craniofacial malformations in zebrafish,[82] whereas death and impaired proliferation of neural stem cells probably contributes to microencephaly by reducing the pool of neural progenitor cells, as shown in rodent models.[83,84] Death of proopiomelanocortin neurons in the arcuate nucleus of the rat hypothalamus reduces endorphin inhibition of the hypothalamic–pituitary–adrenal axis, predisposing the rat to stress and altered circadian rhythms.[83] Alcohol-induced endocrine dysfunction, disruption of morphogen signalling, and activation of neuroinflammation can affect the developing brain and have long-term effects on immune and endocrine systems, as shown by rodent and human data.[80,85–88] In-vitro studies show that alcohol disrupts neural cell migration and axon pathfinding by blocking cell adhesion and axon outgrowth mediated by the L1 neural cell adhesion molecule.[89] Notably, mutations in the human *L1CAM* gene cause dysgenesis of the corpus callosum, hydrocephalus, and cerebellar dysplasia, mirroring some fetal alcohol syndrome neuropathological abnormalities.[89,90] In zebrafish, alcohol alters craniofacial and brain development by disrupting *PDGFRA* and its downstream signalling elements, PI3K and mTOR.[91] Genetic polymorphisms in *PDGFRA*, and in genes that regulate the sensitivity of L1 to ethanol, are associated with craniofacial and brain dysmorphology in humans.[89,91]

## Management

Interventions for fetal alcohol spectrum disorder are multifaceted. The treatment approach accommodates an individual's specific profile of needs (eg, behavioural, cognitive, mental health, and adaptive), in a similar manner to the tailored approach used for other developmental disorders, such as intellectual disability or autism.[67,92] For children and adolescents with fetal alcohol spectrum disorder, interventions might include education and behaviour management training for parents, computerised attentional training, impulse control therapy, special education including literacy and mathematics training, and social skills development.[92] A meta-analysis[93] of interventions for gross motor deficits in children with neurodevelopmental disorders suggested that they had some utility (and could theoretically have benefits for neurodevelopmental problems resulting from prenatal alcohol exposure), but there have been few high-quality clinical trials to date. The management of adult fetal alcohol spectrum disorder is characterised by poor availability of services compared with those available to

children, including shortages of comprehensive assessment, substance-abuse screening and treatment, psychotherapy, suicide prevention, employment assistance, housing assistance, and family or parenting support.[94]

No specific drug treatments for individuals with fetal alcohol spectrum disorder are available, and clinicians often use combinations of dopamine reuptake inhibitors, norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and serotonin receptor antagonists, among other medications, for treatment of comorbid and co-occurring conditions, such as attention-deficit hyperactivity disorder, disorders of impulse control, aggression, and mood disorders.[92] Two small studies (reviewed by Petrenko and Alto[92]) found that stimulants such as methylphenidate and dexamfetamine might be effective at treating hyperactivity in children (5–14 years) with fetal alcohol spectrum disorder, despite not fully addressing inattention and impulsivity.

An emerging treatment approach that is specific to children with fetal alcohol spectrum disorder is targeted nutritional supplementation during key developmental time periods (eg, during the prenatal period and the first 5 years of life).[95,96] A rodent study found that choline supplementation could attenuate the neurodevelopmental effects of prenatal alcohol exposure.[97] A study of prenatal choline supplementation (supplements given to pregnant women consuming alcohol)[96] and a study of postnatal choline supplementation (supplements given to children aged 2–5 years with prenatal alcohol exposure)[95] suggest potential benefits for recognition memory and sequential memory. An educational intervention called Math Interactive Learning Experience that is specifically designed for individuals with fetal alcohol spectrum disorder has been shown to address mathematical learning disability, resulting in improved achievement in mathematics,[98] suggesting that early identification of fetal alcohol spectrum disorders and targeted educational interventions might improve patient outcomes.

## Conclusions and future directions

Fetal alcohol spectrum disorder, caused by prenatal alcohol exposure, is a global public health problem that is under-recognised and underdiagnosed despite high prevalence and burden to society.[3,4,6] Prenatal alcohol exposure, a common teratogenic event, leads to cardinal craniofacial abnormalities (eg, small palpebral fissures, flattened philtrum, and thin upper lip) in some cases,[1,26] and a range of neuropathological abnormalities and associated cognitive, behavioural, and social impairments.[4,8,36,74] More than 45 years of basic science evidence has shown that prenatal alcohol exposure disrupts critical neurodevelopmental processes,[12,80,83] and human studies show the effects on brain structure, brain function, and cognition.[8,40,57] Social stigma, inadequate awareness of fetal alcohol spectrum disorder and its frequency, and a low capacity for screening and diagnosis result in children exposed to prenatal alcohol being underdiagnosed, and diagnosis is rare in adults.[27] Different diagnostic systems and disagreements over the thresholds of prenatal alcohol exposure at which adverse effects occur have contributed to the wide variation in diagnosis and case identification globally.[62,99] An internationally accepted diagnostic system is needed to advance research and clinical care of individuals with fetal alcohol spectrum disorder.

An awareness of the clinical presentations of fetal alcohol spectrum disorder will enable neurologists and other health-care professionals to assist patients through education, comorbidity assessment, and referrals.[26,32,38] Automated tools that can be accessed online or via mobile applications are currently under development and will broaden fetal alcohol spectrum disorder diagnosis and treatment. Three-dimensional imaging, which is increasingly possible with smartphones, can already distinguish children with heavy prenatal alcohol exposure (14 or more drinks per week, or five or more drinks per occasion) from healthy controls by recognising subtle facial features, with 97% specificity for fetal alcohol syndrome and 90% specificity for partial fetal alcohol syndrome.[10] Because face and brain development are linked,[12] the detection of subtle facial dysmorphology can predict neurocognitive impairment, even in children without fetal alcohol spectrum disorder cardinal facial features. Similarly, scalable tools that use two-dimensional facial images can distinguish children with alcohol-related neurodevelopmental disorder from non-exposed children, potentially facilitating high-throughput screening for fetal alcohol spectrum disorder in the future.[100] These automated tools might eventually even allow for detection of craniofacial and neurodevelopmental abnormalities caused by lower levels of prenatal alcohol exposure,[101] which could decrease the dependence on a documented history of prenatal alcohol exposure or the skills of dysmorphologists in the diagnosis of fetal alcohol spectrum disorder. Neuropsychological and behavioural evaluation, which is important for quantifying cognitive deficits in individuals with fetal alcohol spectrum disorder, is time-consuming and not always available because of a limited number of clinicians in the field. Therefore, rapid neurobehavioural screening tools will aid clinicians. For instance, a decision tree that relates to a few key neurocognitive and behavioural variables is currently in a pilot stage.[11]

Improvements in diagnosis should ideally be accompanied by increased availability of treatment.[69,94] With increased diagnostic capacity through automated facial characterisation and rapid cognitive evaluation, semi-automated cognitive interventions that can be scaled to reach more individuals with fetal alcohol spectrum disorders will become essential. Computerised cognitive training, which is an increasingly common intervention for neurocognitive deficits, improves attention and working memory in children with fetal alcohol spectrum disorder[102] and is a potentially scalable treatment for this disorder. Behavioural interventions and training of parents

### Search strategy and selection criteria

We searched PubMed and the Cochrane Library for articles published in English between Jan 1, 2013, to Dec 15, 2018 with the search terms "fetal alcohol syndrome", "fetal alcohol spectrum disorder", "alcohol-related neurodevelopmental disorder", and "prenatal alcohol". We also identified articles through reference lists, review articles, the authors' own published research, and textbooks. The final reference list was generated on the basis of the relevance of papers to the topics that are discussed in this Review.

in the management of challenging child behaviours will help to address the many behavioural complications caused by prenatal alcohol exposure.[92] Randomised controlled trials[95,96] assessing nutritional interventions showed that targeting specific neural systems during prenatal and postnatal development is possible, and these interventions have the potential to directly address the effects of prenatal alcohol exposure, as well as being scalable.

In the near future, we expect to see increased awareness of the dangers of prenatal alcohol exposure, new public health initiatives to reduce exposed pregnancies, more efficient and widely available diagnostic tools, and treatments that target the effects of prenatal alcohol exposure at multiple levels of functioning.

#### Contributors

All authors contributed equally to the conceptual development, literature review, and drafting and revision of this paper. All authors have approved the submitted version.

#### Declaration of interests

JRW, EPR, and MEC received grant funding from the US National Institute on Alcohol Abuse and Alcoholism during the writing of this review. EPR is on the Board of Directors of the National Organization on Fetal Alcohol Syndrome, although he is not compensated for his board service. MEC reports receiving grant funding from the Medical Research Service of the Department of Veteran Affairs during the writing of this review. MEC also receives royalties from a chapter in UpToDate on neurological complications of alcoholism. MEC holds two US patents related to compounds that block the effects of alcohol on the L1 cell adhesion molecule and decrease the teratogenic effects of alcohol: US6359015B1 and US6977272B2.

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