nature reviews disease primers

https://doi.org/10.1038/s41572-023-00420-x

Primer

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Fetal alcohol spectrum disorders

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Abstract

Alcohol readily crosses the placenta and may disrupt fetal development. Harm from prenatal alcohol exposure (PAE) is determined by the dose, pattern, timing and duration of exposure, fetal and maternal genetics, maternal nutrition, concurrent substance use, and epigenetic responses. A safe dose of alcohol use during pregnancy has not been established. PAE can cause fetal alcohol spectrum disorders (FASD), which are characterized by neurodevelopmental impairment with or without facial dysmorphology, congenital anomalies and poor growth. FASD are a leading preventable cause of birth defects and developmental disability. The prevalence of FASD in 76 countries is >1% and is high in individuals living in out-of-home care or engaged in justice and mental health systems. The social and economic effects of FASD are profound, but the diagnosis is often missed or delayed and receives little public recognition. Future research should be informed by people living with FASD and be guided by cultural context, seek consensus on diagnostic criteria and evidence-based treatments, and describe the pathophysiology and lifelong effects of FASD. Imperatives include reducing stigma, equitable access to services, improved quality of life for people with FASD and FASD prevention in future generations.

Sections

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Introduction

Alcohol consumption has occurred for centuries, with harms from prenatal alcohol exposure (PAE) being mentioned in Greek and biblical verses and depicted in the art and literature of the eighteenth and nineteenth centuries[1,2]. A French-language publication from 1968, which received little attention at the time, described perinatal death, prematurity, growth retardation, facial features and malformations in the offspring of women who consumed alcohol during pregnancy[3]. Unaware of the French publication, Jones et al. described a similar pattern of altered morphogenesis and function in 11 children of mothers with 'alcoholism' in the *Lancet* in 1973 (ref. [4]). They reported specific facial features (thin upper lip, smooth philtrum (the vertical groove between the base of the nose and the border of the upper lip) and short palpebral fissures) and coined the term fetal alcohol syndrome (FAS)[5]. By 1977, the US government had issued a warning about the health risks of alcohol use during pregnancy, which was endorsed by professional organizations in the USA[6,7]. In 1981, the US Surgeon General issued stronger advice that "women who are pregnant (or considering pregnancy) not drink alcoholic beverages"[8] and other countries subsequently issued similar advice. The teratogenic effects of alcohol were subsequently confirmed in animal studies[9].

Later studies found that, in addition to FAS, PAE could cause behavioural, cognitive and learning problems, such as attention deficit hyperactivity disorder (ADHD) and speech and language delay, in the absence of facial and other physical features[10]. Recognition of the disconnect between the neurodevelopmental and physical effects (which relate to first-trimester exposure) of PAE and the wide range of outcomes caused by PAE led to the introduction of the term fetal alcohol spectrum disorders (FASD)[11]. Subsequent research identified groups at increased risk of FASD[12] and associations between FASD and metabolic, immunological and cardiovascular diseases in adults[13,14].

FASD occur in all socioeconomic and ethnic groups[15] and are complex, chronic conditions that affect health and family functioning[16]. Individuals with FASD usually require lifelong health care as well as social and vocational support. Some require remedial education and others interact with the justice system. Early diagnosis and a strength-based management approach will optimize health outcomes.

FASD are the most common of the potentially preventable conditions associated with birth anomalies and neurodevelopmental problems[13], and their global effects, including huge social and economic costs, are substantial[17]. For example, in Canada, the annual cost associated with FASD is an estimated ~CAD$ 1.8 billion (CAD$ 1.3 billion to CAD$ 2.3 billion)[17], which is attributable in part to productivity loss (41%), correction services (29%) and health care (10%). In North America, the lifetime cost of supporting an individual with FASD is estimated at >CAD$ 1 million[18]. Addressing and preventing alcohol use in pregnancy is a public-health imperative.

This Primer presents the epidemiology of FASD and the latest understanding of its pathophysiology as well as approaches to diagnosis, screening and prevention. The Primer also describes outcomes across the lifespan, management and quality of life (QOL) of people living with FASD, and highlights important areas for future research and clinical practice.

Epidemiology

Alcohol use during pregnancy

No safe level of PAE has been established[19], and international guidelines advise against any amount or type of alcohol use during pregnancy[20–23]. Nevertheless, ~10% of pregnant women worldwide consume alcohol[24,25]. The highest prevalence of alcohol use during pregnancy is in the WHO European Region (25.2%[24]; Fig. 1), consistent with the prevalence of heavy alcohol use, heavy episodic drinking and alcohol use disorders in this region[26].

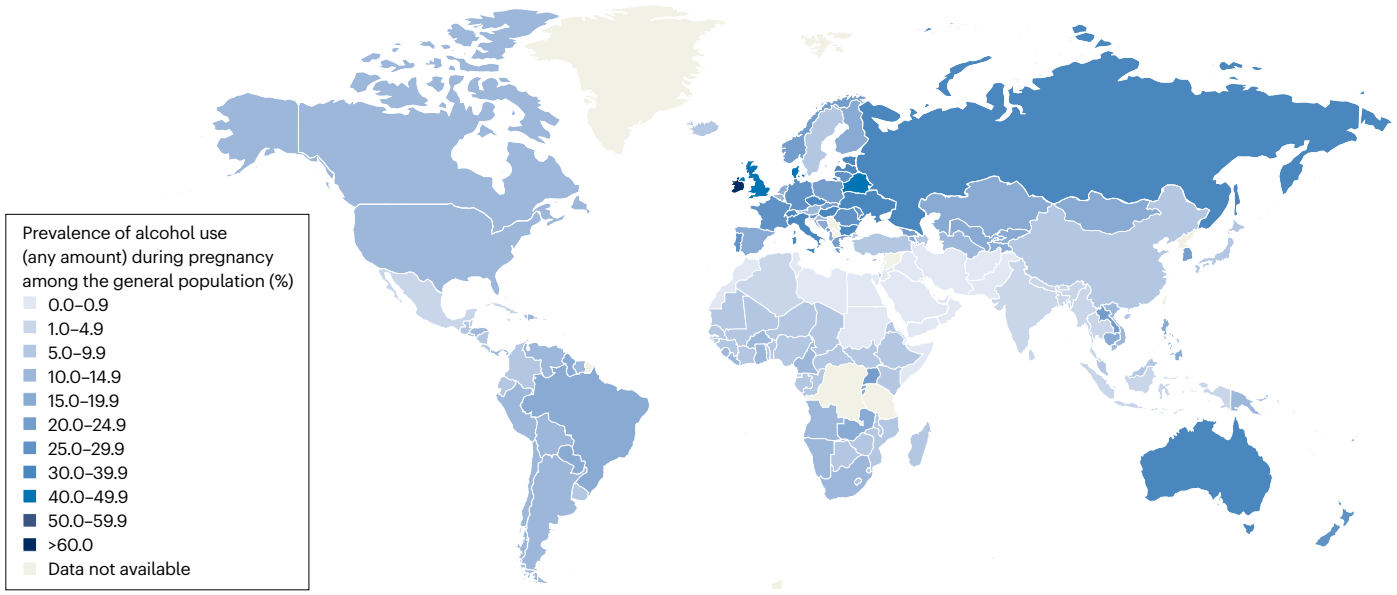

Fig. 1 | Prevalence of alcohol use (any amount) during pregnancy among the general population (%). The highest pooled prevalence (%) of alcohol use during pregnancy in the general population is estimated in the WHO European Region (25.2%, 95% CI 21.6–29.6), followed by the Region of the Americas (11.2%, 95% CI 9.4–12.6), the African Region (10.0%, 95% CI 8.5–11.8), the Western Pacific Region (8.6%, 95% CI 4.5–11.6) and the South-East Asia Region (1.8%, 95% CI 0.9–5.1), and the lowest prevalence is estimated in the Eastern Mediterranean Region (0.2%, 95% CI 0.1–0.9), where most of the population is of Muslim faith and the rates of abstinence from alcohol are very high. The pooled global prevalence of alcohol use during pregnancy in the general population is estimated at 9.8% (95% CI 8.9–11.1). Data from ref. [24].

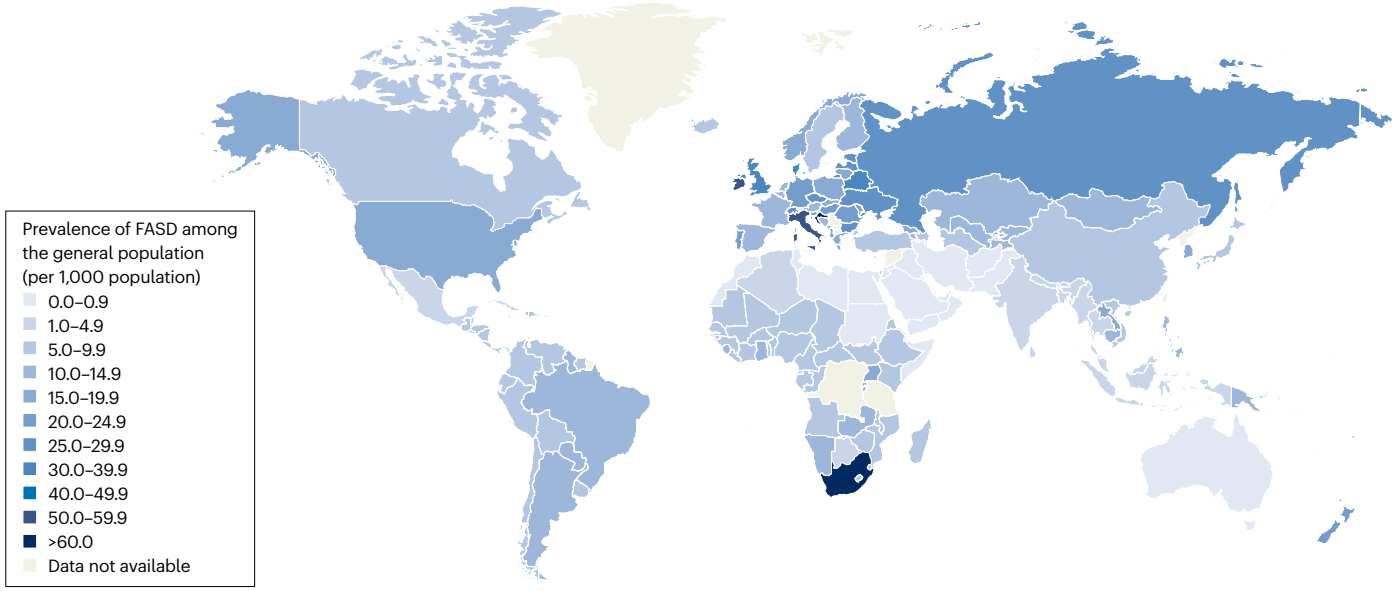

Fig. 2 | Prevalence of FASD among the general population (per 1,000 population). In line with the prevalence of alcohol use during pregnancy, the highest pooled prevalence (per 1,000) of fetal alcohol spectrum disorders (FASD) was in the WHO European Region (19.8 per 1,000 population, 95% CI 14.1–28.0), followed by the Region of the Americas (8.8 per 1,000 population, 95% CI 6.4–13.2), the African Region (7.8 per 1,000 population, 95% CI 5.4–10.7), the Western Pacific Region (6.7 per 1,000 population, 95% CI 4.5–11.7) and the South-East Asia Region (1.4 per 1,000 population, 95% CI 0.6–5.3), and the lowest prevalence was estimated in the Eastern Mediterranean Region (0.1 per 1,000 population, 95% CI 0.1–0.5). The pooled global prevalence of FASD was estimated to be 7.7 (95% CI 4.9–11.7) per 1,000 in the general population. Data from refs. [25,48].

In 40% of the 162 countries evaluated, >25% of women who consumed any alcohol during pregnancy drank at 'binge' levels (defined as ≥4 US standard drinks containing 14 g of pure alcohol per drink on a single occasion). Binge drinking, which increases the risk of FASD, is common in early pregnancy and before pregnancy recognition[25,27]. Many fetuses are inadvertently exposed to alcohol because binge drinking is prevalent in young women, millions of women who consume alcohol report having unprotected sex and approximately half of all pregnancies are unplanned[28–31]. Alcohol use during pregnancy is higher in certain subpopulations, including some Indigenous populations in Australia (55%)[32], South Africa (37%)[33] and Canada (60%)[34], often in the context of disadvantage, violence and ongoing traumatic effects of colonization[35].

Risk factors for maternal alcohol consumption. Various risk factors have been identified for maternal alcohol use in pregnancy, including higher gravidity and parity[36], delayed pregnancy recognition, inadequate prenatal care or reluctance of health professionals to address alcohol use[37,38], a history of FASD in previous children[38], alcohol use disorder and other substance use (including tobacco)[39], mental health disorders (such as depression)[39], a history of physical or sexual abuse, social isolation (including living in a rural area during pregnancy), intimate partner violence[38,40], alcohol and/or drug use during pregnancy by the mother's partner[38,41] or other family members[38,41], and poverty[42].

Risk factors for alcohol use during pregnancy vary across countries and throughout the course of pregnancy. For example, in Australia, first-trimester alcohol use was associated with unplanned pregnancy[43], age <18 years at first intoxication[30], frequent and binge drinking in adolescence[44], and current drinking and a tolerant attitude to alcohol use in pregnancy[45]. Women who continued to drink alcohol throughout pregnancy were more likely to be older, have higher socioeconomic status, salary and educational levels, smoke, have a partner who consumes alcohol, and have an unintended pregnancy than those who abstained, and were less likely to agree with guidelines that recommend avoiding alcohol use in pregnancy[30,31,46,47].

FASD prevalence

The estimated global prevalence of FASD among the general population is 7.7 cases per 1,000 individuals[25,48]. Consistent with rates of alcohol use during pregnancy, FASD prevalence (Fig. 2) is highest in the WHO European Region (19.8 per 1,000) and lowest in the WHO Eastern Mediterranean Region (0.1 per 1,000)[25,48]. In terms of individual countries, South Africa (111.1 per 1,000), Croatia (53.3 per 1,000), Ireland (47.5 per 1,000), Italy (45.0 per 1,000) and Belarus (36.6 per 1,000) have the highest FASD prevalence, whereas Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates have no recorded cases of FASD[25,48]. Furthermore, 76 countries have a prevalence of FASD of >1%[25,48], which exceeds the prevalence of neurodevelopmental conditions, including Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), spina bifida and anencephaly in the USA[49], and is similar to the prevalence of autism spectrum disorders (1.1–2.5%)[50].

Based on global epidemiological data, an estimated 1 in 13 women who consume alcohol while pregnant will deliver a child with FASD, resulting in the birth of ~630,000 children with FASD globally every year[48]. FASD confers lifelong disability, and an estimated >11 million individuals aged 0–18 years and 25 million aged 0–40 years have FASD[51].

A systematic review and meta-analysis revealed that FASD prevalence is 10–40 times higher in some subpopulations than in the general population, including in children in out-of-home care and correctional,

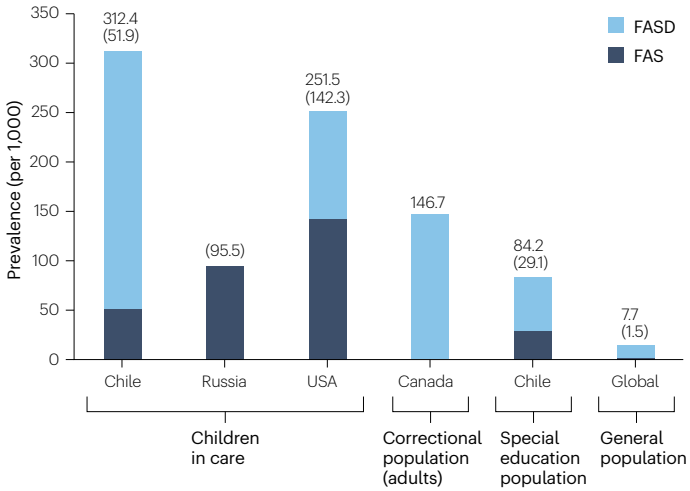

Fig. 3 | Pooled prevalence of FASD and FAS (shown in brackets) among selected subpopulations, by country, and in the general global population. The pooled prevalence (per 1,000) of fetal alcohol spectrum disorders (FASD) is markedly higher in some subpopulations than in the general global population. Subpopulations with a high prevalence of FASD include children in out-of-home care, individuals involved with correctional services and those receiving special education. FAS, fetal alcohol syndrome.

special education, and specialized clinical settings[12] (Fig. 3). The pooled prevalence of FASD among children in out-of-home or foster care is 25.2% in the USA and 31.2% in Chile (32-fold and 40-fold higher than the global prevalence, respectively)[12]. FASD prevalence among adults in the Canadian correctional system (14.7%) is 19-fold higher than in the general population, and the prevalence among special education populations in Chile (8.4%) is over 10-fold higher than in the general population[12]. Moreover, the prevalence of FASD is 62% among children with intellectual disabilities in care in Chile[52], >50% in adoptees from Eastern Europe[53,54] and ~40% among children in Lithuanian orphanages[55]. The prevalence of FASD is 36% in one Australian youth correctional service[56], >23% in Canadian youth correctional services[57], >14% among USA populations in psychiatric care[58] and 19% in some remote Australian Indigenous communities[59]. The highest prevalence estimates for FAS (46–68%) are in children with developmental abnormalities in Russian orphanages[60]. The high prevalence of FASD in some subpopulations has prompted calls for targeted screening in these groups.

Mechanisms/pathophysiology

Alcohol rapidly equilibrates between the maternal and fetal compartments and is eliminated primarily through maternal metabolism[61]. As previously mentioned, no safe level of PAE has been established[19]. Several developmentally important molecular targets of alcohol, including the L1 neural cell adhesion molecule and $GABA_A$ receptors, are disrupted at blood alcohol concentrations attained after one or two US standard drinks[62–66]. Hence, repeated exposure to low levels of alcohol or a single exposure at critical periods in gestation could affect development. Indeed, drinking ≤20 g of alcohol per occasion (≤1.5 US standard drinks) or ≤70 g alcohol per week (≤5 US standard drinks) was associated with mild facial dysmorphology (determined via 3D facial imaging)[67], microstructural brain abnormalities, and externalizing behaviours such as aggression and violation of social norms[68]. The Adolescent Brain Cognitive Development (ABCD) Study, a large, prospective, longitudinal study of child and adolescent development, reported a dose-dependent association between low-level drinking during pregnancy, increased cerebral volume and regional cortical surface area, and a range of adverse cognitive, psychiatric and behavioural outcomes in children aged 9–10 years[69]. There was no inflexion point in the dose–response curves to suggest a cut-off for PAE effects, and significant effects were observed with as little as 1.1 US standard drinks per week throughout pregnancy. Increased brain volume was attributed to impairment of synaptic pruning in the preadolescent brain, consistent with research demonstrating the effect of PAE on trajectories of brain development[70,71].

Genes associated with PAE

Several gene variants confer heightened risk or resilience to PAE[72–74], and there is higher concordance for FAS among monozygotic than among dizygotic twins[74]. Genetic effects may be exerted through the mother and/or the fetus[72]. *ADH1* (encoding alcohol dehydrogenase 1) polymorphisms, such as *ADH1B*2* and *ADH1B*3*, which increase alcohol metabolism and decrease blood alcohol levels, are associated with reduced risk of FASD[72]. Moreover, zebrafish with *pdgfra* (encoding platelet-derived growth factor receptor-α) haploinsufficiency have increased susceptibility to craniofacial malformations caused by PAE, which is mirrored in individuals with *PDGFRA* polymorphisms[75]. Similarly, haploinsufficiency of either *Shh* or *Gli2* (a downstream effector of *Shh*) is clinically silent in mice; however, PAE in these mice results in midline craniofacial malformations[76]. Interestingly, hypermethylation of *GLI2* (which decreases *GLI2* expression) was identified in genome-wide DNA methylation profiling of children with FASD[77]. Prenatal or postnatal choline supplementation improves cognition in animal models and clinical studies[78] and the effect of choline supplementation is modified by polymorphisms in *SLC44A1* (encoding choline transporter-like protein 1)[79].

Timing and quantity of PAE during gestation

The effects of PAE vary according to the quantity, frequency, duration, pattern and timing of exposure[80]. Periconceptional alcohol exposure can adversely affect fetal development and predispose to disease in later life[81,82]. PAE at different stages of organogenesis has distinct developmental consequences. PAE during first-trimester organogenesis may cause brain, craniofacial, skeletal and internal organ dysmorphology[80]. In mice, PAE during gastrulation (equivalent to the third week post-fertilization in humans, when an embryo transforms from a bilaminar disc to a multilayered structure comprising the three primary germ layers: ectoderm, mesoderm and endoderm) reproduces the sentinel craniofacial abnormalities of FAS: thin upper lip, smooth philtrum and short palpebral fissures[9] (Fig. 4). By contrast, alcohol exposure during neurulation (starting in gestational week three in humans, resulting in the folding of the neural plate to form the neural tube) produces a facial phenotype that resembles DiGeorge syndrome, a chromosomal disorder (22q11.2 deletion) associated with facial anomalies, immune dysfunction, cardiac defects and neurodevelopmental abnormalities[83].

The brain is vulnerable to PAE throughout pregnancy[84,85]. PAE after 8 weeks of gestation affects neurogenesis, differentiation of neural precursor cells, neuronal migration, pathfinding, synaptogenesis and axon myelination[72,85,86] but does not cause sentinel craniofacial dysmorphology or major organ defects. Thus, PAE after major organogenesis may result in a FASD phenotype with neurodevelopmental disorder but

without physical alterations, making diagnosis difficult[80]. Nutritional deficiency during pregnancy may potentiate the effects of PAE on developmental outcomes, and maternal alcohol intake may further reduce the availability of developmentally important nutrients[87].

Effects of PAE on the embryo and fetus

Brain development. As previously mentioned, PAE can affect brain development[88,89]. Retrospective examination of 149 brains from individuals with PAE who died between birth and adulthood identified gross abnormalities in brain development causing microcephaly (a smaller than normal head for age and sex using population-based normative data, often associated with a smaller than normal brain (micrencephaly)) in 20.8%. This study found isolated hydrocephalus in 4.0% of individuals with PAE, corpus callosum defects in 4.0%, prenatal ischaemic lesions in 3.4%, minor subarachnoid heterotopias (the presence of normal tissue at an abnormal location, such as an ectopic cluster of neurons within the white matter, often due to abnormal neuronal migration during early brain development) in 2.7%, holoprosencephaly (whereby the embryonic forebrain fails to develop into two discrete hemispheres, often affecting midline brain and craniofacial structures) in 0.7% and lissencephaly (smoothness of the brain surface due to impaired development of cerebral gyri) in 0.7%[88]. Hence, because macroscopic neuropathology is not present in most individuals with FASD, microscopic neuropathology likely underlies many of the associated cognitive and behavioural abnormalities of this disorder. Studies in non-human primates show that first-trimester-equivalent alcohol exposure reduces brainstem and cerebellar volume and disrupts various white matter tracts, including one connecting the putamen and primary sensory cortex[90]. Third-trimester-equivalent alcohol exposure reduced hippocampal neuronal numbers in infant and juvenile Vervet monkeys[86].

Brain structure. Relatively few macroscopic brain lesions have been identified in clinical neuroimaging studies of children with FASD[80,91]. Blind evaluation of clinical MRI studies by neuroradiologists identified clinically significant abnormalities in 3% of individuals with PAE or FASD and in 1% of typically developing controls[91]. Four of 61 patients with FAS had heterotopias[92]. By contrast, quantitative research imaging studies in groups of children with PAE and FASD have revealed region-specific increases or decreases in grey matter thickness, microstructural white matter abnormalities, and neuronal and glial migration defects[69,93,94]. Volume reduction is disproportionate in the cerebrum, cerebellum, caudate, putamen, basal ganglia, thalamus and hippocampus after accounting for overall reductions in brain volume[94]. Age-dependent decreases in cortical gyrification are also observed[94–96] and the corpus callosum can be hypoplastic, posteriorly displaced or, in rare cases, absent[94,97–100]. Moreover, studies using diffusion tensor imaging reveal reduced integrity of large white matter tracts, including in the corpus callosum, cerebellar peduncles, cingulum and longitudinal fasciculi[101]. Hypoplasia of the corpus callosum in children with FASD is associated with impaired interhemispheric transfer of information[102].

Imaging studies have also demonstrated the effect of PAE on postnatal grey matter development[99,103]. Typical brain development is associated with a large increase in cortical grey matter during early childhood followed by loss of cortical grey matter during late childhood and adolescence via synaptic pruning, a process that reflects cortical plasticity[70]. By contrast, children with FASD show region-specific loss of grey matter and decreased gyrification from early childhood through

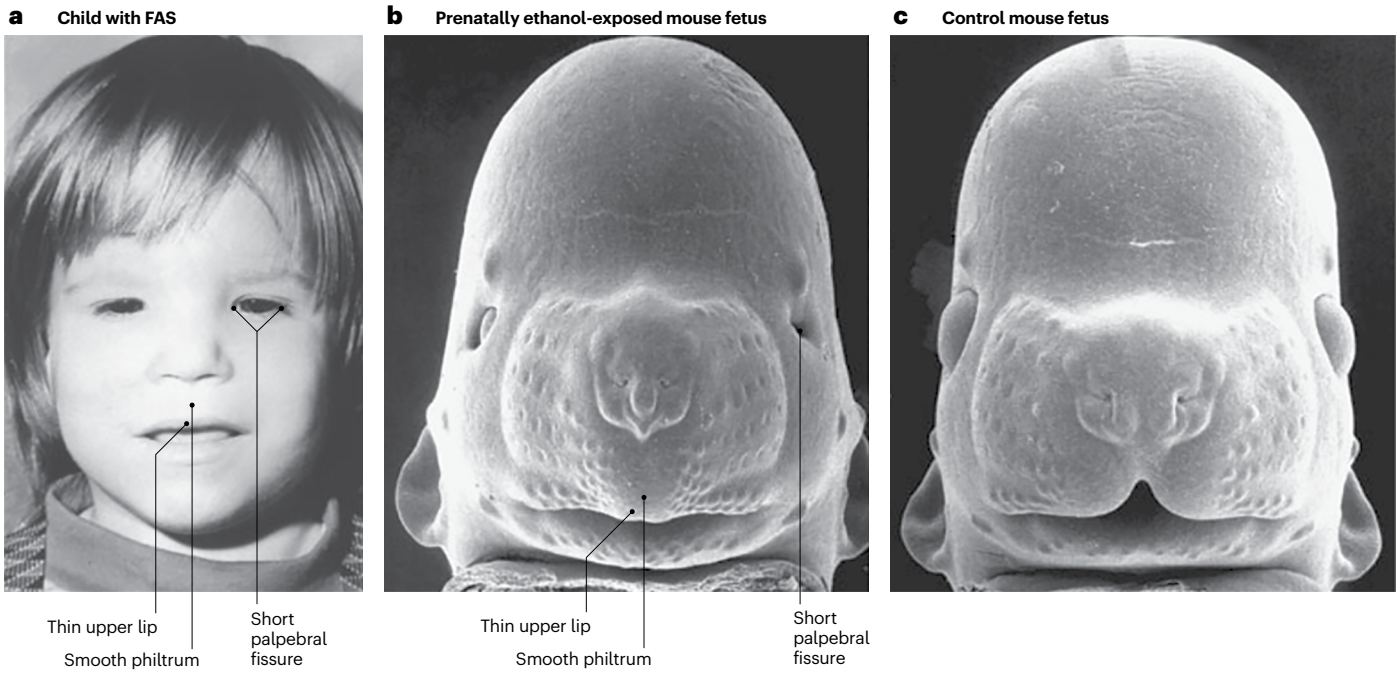

Fig. 4 | Prenatal alcohol exposure during gastrulation in mice reproduces the facial phenotype of FAS. a,**b**, The facial phenotype of fetal alcohol spectrum disorders can be reproduced in a preclinical model. Comparable to the facial features of the child with fetal alcohol syndrome (FAS) (part **a**), the mouse fetus exposed prenatally to alcohol shows a thin upper lip with a smooth philtrum, short palpebral fissures and a small midface (part **b**). **c**, The normal features in a control mouse fetus (not prenatally exposed to alcohol). Part **a** courtesy of Sterling Clarren. Parts **b** and **c** adapted with permission from ref. [9], AAAS.

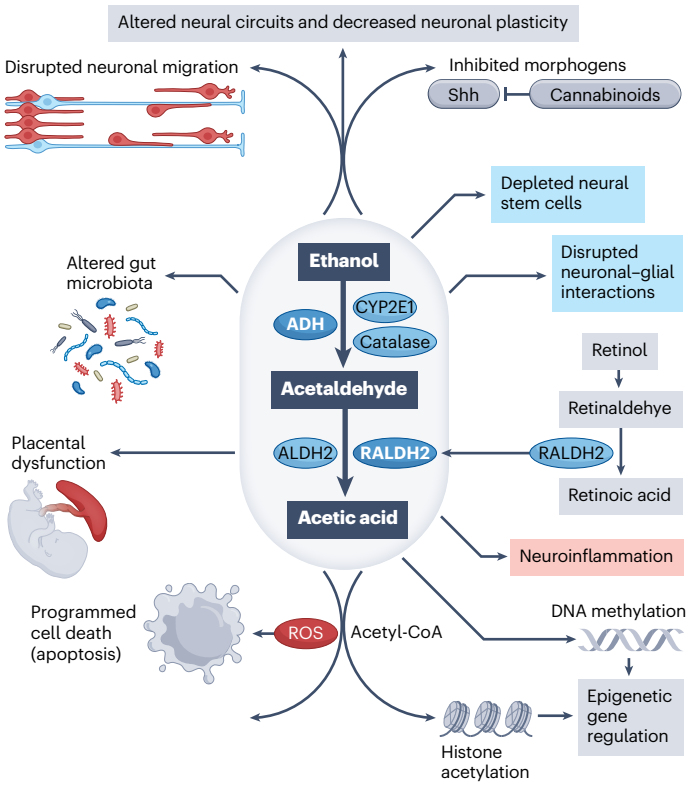

Fig. 5 | Mechanisms of alcohol teratogenesis. Alcohol (ethanol) metabolism to acetaldehyde and acetic acid generates reactive oxygen species (ROS) that induce programmed cell death. During gastrulation, acetaldehyde competes with retinaldehyde for metabolism by retinaldehyde dehydrogenase 2 (RALDH2), reducing the biosynthesis of retinoic acid, a critical morphogen. Acetyl-CoA, a metabolite of acetic acid, acetylates histones and, therefore, modifies gene expression. Alcohol also alters epigenetic gene regulation through changes in DNA methylation. Moreover, alcohol disrupts neuronal–glial interactions, induces inflammatory changes in the developing brain and causes microencephaly partly by depletion of neural stem cells. Other effects of alcohol include the disruption of Shh signalling (an effect that is potentiated by cannabinoids) and disrupted neuronal migration. The effects of alcohol on the placenta contribute to intrauterine growth retardation and adverse neurodevelopmental outcomes. Modification of gut microbiota by alcohol may influence brain development through the action of circulating microbial by-products. Collectively, these actions of alcohol result in altered neural circuits and decreased neuronal plasticity. ADH, alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase.

adolescence[70,99,102]. This change may partly explain contradictory findings of increased or decreased grey matter volume in various studies, which sampled different brain regions during distinct developmental periods or evaluated populations with different levels of PAE[69]. A relatively small sample size is another source of variation in results among brain imaging studies[104].

One frequently observed effect of PAE is the disruption of brain plasticity[105]. Animal models and human studies have demonstrated enduring deficits in learning and memory following PAE, associated with abnormal plasticity in hippocampal, thalamic, cortical and cerebellar circuits[105–107]. These deficits are associated with changes in alpha oscillations on magnetoencephalography, fractional anisotropy (a measure of white matter integrity) on diffusion tensor imaging, and functional and resting-state MRI in children with PAE[68,94,108,109].

Craniofacial development. Brain and craniofacial development are mechanistically linked; therefore, brain and craniofacial abnormalities frequently co-occur[98,110]. For example, abnormalities of midline brain structures, such as the corpus callosum, diencephalon and septum, are associated with midline craniofacial abnormalities[98,103,110]. Craniofacial development relies on the highly choreographed migration of cranial neural crest cells and is most sensitive to PAE during the third week of gestation. Alcohol induces apoptosis of neural crest cells through oxidative injury and disruption of Sonic hedgehog (Shh) signalling[111]. Shh regulates embryonic morphogenesis and organogenesis, including the organization of cells of the central nervous system (CNS), limbs and other body parts. In animal models, diverse antioxidants and inhibitors of apoptosis mitigate the effects of alcohol on neural crest cells[112,113].

Mechanisms of alcohol teratogenesis

Multiple mechanisms of alcohol-induced teratogenesis have been elucidated[9,80,114,115] (Fig. 5). Alcohol has protean effects on brain and craniofacial development in part because it is a weak drug that requires millimolar concentrations to produce even mild euphoria[116]. For example, in the USA, legal intoxication is defined as 17.4 mM or 0.08 g/dl; at these high concentrations, alcohol interacts with diverse molecules and signalling pathways that regulate development[117].

Epigenetic changes and disrupted development. Epigenetic changes are chemical modifications (methylation or acetylation) to DNA and surrounding histones that influence gene expression and often occur in response to environmental exposures[118,119]. Normal development depends on numerous epigenetic changes in embryonic stem cells that facilitate their transition to fully differentiated and functional cell lineages such as neurons, muscle and fat cells[120]. Alcohol can disrupt development by inducing DNA methylation and histone acetylation in gene clusters and altering gene expression[121]. Epigenetic alterations resulting from PAE have been observed in animal models and humans, and these changes may be lifelong and inherited by future generations[118,122–124]. A pattern of DNA methylation in buccal epithelial cells was reasonably accurate (positive predictive value 90%; negative predictive value 78.6%) in discriminating children with FASD from typically developing controls or children with autism spectrum disorders[125]. Large replication studies in different populations are required before this approach might be considered for diagnostic purposes.

Brain injury. Exposure of astrocytes to alcohol and metabolism of alcohol by cytochrome P450 2E1 result in the production of damaging reactive oxygen species[84,126]. Alcohol is metabolized to acetaldehyde, a toxin that causes DNA damage, epigenetic gene regulation, mitochondrial and proteosome dysfunction, and altered cellular metabolism[127–129]. Metabolism of acetaldehyde to acetate and then to acetyl-CoA modifies gene expression in the brain via increased histone acetylation[121] (Fig. 5).

Disruption of morphogens and growth factors. Retinoic acid is a critical morphogen (a signalling molecule that alters cellular responses to modulate patterns of tissue development), and its deficiency causes craniofacial defects similar to those of FASD[127,130]. Retinol is oxidized to retinaldehyde, which is subsequently oxidized by retinaldehyde dehydrogenase 2 (RALDH2) to retinoic acid (Fig. 5). During gastrulation, RALDH2 is the predominant enzyme for acetaldehyde metabolism.

Therefore, acetaldehyde and retinaldehyde compete for RALDH2, reducing the synthesis of retinoic acid and inducing a state of retinoic acid deficiency, thereby promoting craniofacial defects associated with PAE[127,130].

Another critical morphogen, Shh, is a downstream target of retinoic acid[72,130]. Genetic abnormalities of the Shh pathway cause holoprosencephaly syndrome, which is associated with abnormal midline craniofacial and brain development similar to that of FASD[72,76]. Alcohol exposure in chick embryos decreases *Shh* expression and induces craniofacial dysmorphology and cranial neural crest cell death; viral vector-mediated expression of *Shh* rescues these effects[111]. Alcohol exposure during neurulation of the mouse rostroventral neural tube disrupts the function of cilia, which transduce Shh signals by modulating the expression of genes that regulate ciliogenesis, protein trafficking and stabilization of primary cilia[131,132]. The associated dysmorphology in zebrafish can be mitigated by activating downstream elements in the Shh signalling pathway[133]. Alcohol also decreases cellular stores of cholesterol, thereby reducing the covalent binding of cholesterol to Shh (which is necessary for Shh secretion and function)[72,134]. These findings suggest that alcohol causes a transient ciliopathy, secondarily disrupting Shh signalling within cilia and producing craniofacial and brain dysmorphology[131].

Disruption of neuronal and glial migration. PAE is associated with macroscopic and microscopic evidence of impaired neuronal and glial migration, including heterotopias (collections of aberrantly migrated neurons). Heterotopias are associated with seizures, and seizures or abnormal EEG results are reported in up to 25% of individuals with FASD[135]. The L1 neural cell adhesion molecule regulates neuronal migration, axon fasciculation and pathfinding in the developing brain[136]. Mutations in *L1CAM* (which encodes L1) cause neurodevelopmental abnormalities such as those observed in FASD, including hydrocephalus, hypoplasia or agenesis of the corpus callosum, and dysplasia of the anterior cerebellar vermis[64]. Alcohol inhibits L1-mediated cell adhesion by binding to specific amino acids at a functionally important domain in the extracellular portion of L1 (ref. [137]). The sensitivity of L1 to alcohol is regulated by phosphorylation, which promotes L1 association with the cytoskeleton[62,138]. Importantly, molecules that block alcohol inhibition of L1 adhesion prevent the teratogenic effects of alcohol in mouse embryos[62,139].

GABAergic interneurons comprise the principal inhibitory network of the brain. Alcohol enhances $GABA_A$ receptor-mediated depolarization of migrating GABAergic interneurons through activation of L-type voltage-gated calcium channels, thereby accelerating tangential migration[63]. Dysfunction of GABAergic interneurons may impair inhibitory control of brain networks. In mice, PAE during corticogenesis also disrupts radial migration and pyramidal cell development in the somatosensory cortex, which could be linked to decreased tactile sensitivity during adolescence[140].

Effects on neural stem cells. Effects of PAE on neural stem cells (NSCs) may contribute to reduced brain volume in individuals with FASD. Alcohol causes cell death in differentiated neural cells but not in NSCs; rather, PAE depletes NSCs by blocking their self-renewal and accelerating their transition into more mature neural progenitors and differentiation into astroglial lineages[141]. PAE also selectively upregulates gene expression for the calcium-activated potassium channel *Kcnn2* in neural progenitor cells from the motor cortex, and Kcnn2 blockers in adult mice reduced motor learning deficits[142]. Alcohol may trigger the maturation of NSCs by increasing the release of selected microRNAs (miRNAs) from extracellular vesicles in NSCs and activating certain pseudogenes that encode non-protein-coding RNAs[141,143]. Proteomic analysis revealed selective enrichment of extracellular vesicles for RNA-binding and chaperone proteins in alcohol-exposed NSCs[144].

Disruption of neuronal–glial interactions. Brain growth and development are dependent on neuronal–glial interactions[84,85]. PAE decreases the proliferation of radial glial cells partly by decreasing Notch1 and fibroblast growth factor 2 receptor signalling[145]. This altered signalling reduces the density and fasciculation of radial glial fibres, which serve as a scaffold for migrating neurons[85,145]. PAE perturbs the maturation of oligodendroglia in human fetal brains, increasing the expression of markers of early oligodendroglia progenitors (Oct4 and Nanog) and decreasing the expression of markers of mature oligodendroglia (Olig1, Olig2 and myelin basic protein)[146]. Alcohol also increases apoptosis to a greater extent in oligodendroglia than in neurons[146,147]. As myelination is mediated by oligodendroglia, apoptosis of these cells might partly account for the effects of PAE on white matter integrity. The associated upregulation of oligodendroglia-derived chemokines (CXCL1/GRO, IL-8, GCP2/CXCL6, ENA78 and MCP1) could also affect neuronal survival[146]. Astroglial apoptosis is mediated by acetaldehyde toxicity, reactive oxygen species, reductions in the antioxidant glutathione and inflammatory signalling[85].

Neuroinflammation. PAE activates an inflammatory response in the developing nervous system. Alcohol stimulates the production of reactive oxygen species in microglia and astrocytes, leading to neuronal apoptosis[84]. Moreover, alcohol stimulates the production of pro-inflammatory cytokines (such as IL-1β and TNF) and chemokines (such as CCL2 and CXCL1) through enduring epigenetic modifications that sustain a chronic neuroinflammatory response[119] (Fig. 5). Unique networks of pro-inflammatory cytokines in serum from women in the second trimester of pregnancy are markers of PAE and adverse neurodevelopmental outcomes[148]. The persistence of pro-inflammatory cytokines in childhood could predispose to autoimmune and inflammatory conditions later in life[149]. Similarly, PAE may hypersensitize microglia to increased inflammatory signalling, leading to an enduring, heightened neuroinflammatory response[84].

Gut microbiota alterations. PAE may cause enduring changes in the gut microbiota[150], and there is increasing recognition of the interplay between gut microbes and nervous system development and function. In a mouse model of PAE, gut microbial metabolites were detected in maternal plasma, fetal liver and fetal brain[151]. Further research is required to determine how effects of PAE on the gut microbiota influence development and later health.

Placental effects. Not all developmental effects of PAE result from the direct actions of alcohol on the developing nervous system. A retrospective autopsy study reported placental abnormalities in 68% of individuals with PAE or FASD[88]. PAE in humans decreases placental weight, epigenetic marks, vasculature and metabolism[81]. PAE during the first 60 of 168 days of gestation in rhesus macaques caused diminished placental perfusion and ischaemic placental injury from middle to late gestation[152]. RNA sequencing analysis revealed activation of inflammatory and extracellular matrix responses. Rats with PAE demonstrate reduced nitric oxide-mediated uterine artery relaxation, potentially contributing to dysregulation of uterine blood flow and intrauterine

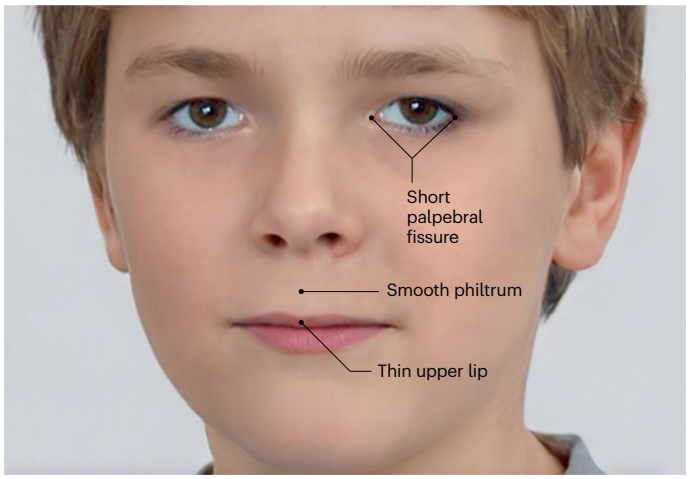

Fig. 6 | Sentinel facial features of fetal alcohol syndrome. Fetal alcohol syndrome has three characteristic (sentinel) facial features: thin upper lip (with absent cupid bow), smooth philtrum (with absence of the normal midline vertical groove and lateral ridges extending from the base of the nose to the vermilion border of the upper lip) and short palpebral fissures (the space between the medial and lateral canthus of the open eye). Image created by Ria Chockalingam using an image from Generated Photos and modified with Adobe Photoshop.

growth retardation[153]. miRNA act by silencing RNA and modifying post-transcriptional regulation of gene expression. A cluster of 11 extracellular miRNA from serum of women in the second trimester of pregnancy was a marker of PAE and predicted adverse neurodevelopmental outcomes in Ukrainian and South African populations[154,155]. Injection of the same 11 miRNAs into pregnant mice decreased placental and fetal growth, suggesting that they mediate the adverse outcomes of PAE[156].

Synergistic effects of alcohol and other substances

PAE is often associated with prenatal exposure to other drugs. Among 174 individuals with PAE, almost all had prenatal nicotine exposure[88]. Nicotine and alcohol synergistically decrease birthweight and increase the risk of sudden infant death syndrome[157]. The legalization of cannabis has led to increases in the combined use of cannabinoids and alcohol during pregnancy[158]. Alcohol and cannabinoids synergistically increase the frequency of ocular defects in mice by disrupting separate elements in the Shh signalling pathway[132]. PAE and opioids each affect neurodevelopment, raising the possibility of additive or synergistic effects[159]. Alcohol also disrupts the developing blood–brain barrier, exposing the developing CNS to drugs and toxins that are normally excluded[160].

Diagnosis, screening and prevention

Diagnosis of FASD

Principles of diagnosis. Diagnosis of FASD requires assessment of PAE, neurodevelopmental function and physical features, including facial features (Fig. 6). Timely, accurate diagnosis of FASD is crucial to enable early intervention and improve outcomes[161], but there is no diagnostic test, biomarker or specific neurodevelopmental phenotype for FASD. Ideally, assessment and diagnosis should be conducted by a multidisciplinary team (MDT) comprising paediatricians, neuropsychologists, speech pathologists, occupational therapists, physiotherapists and social workers, with access to psychiatrists and geneticists/dysmorphologists. However, this approach is expensive, time consuming and unavailable to many children worldwide. Often, children present first to family physicians, paediatricians and psychologists who lack sufficient expertise to confidently diagnose FASD. Thus, education and training are urgently needed to increase the capacity for recognition of FASD outside specialist FASD assessment services[51,162] and to address its underdiagnosis and misdiagnosis[163,164].

Approaches to the diagnosis of FASD. The most commonly used diagnostic systems for FASD are the Collaboration on FASD Prevalence (CoFASP) Clinical Diagnostic Guidelines[10], the University of Washington 4-Digit Diagnostic Code[165,166] and the Canadian Guidelines[167] (Table 1). The Canadian Guidelines have been adapted for use in Australia[168] and the UK[169] and are also used in New Zealand[170]. Guidelines have also been recommended by the US Centers for Disease Control and Prevention[171], the State Agency for Prevention of Alcohol-Related Problems (PARPA) in Poland[172], and The German Federal Ministry of Health[173].

All diagnostic systems recommend evaluating PAE, facial and non-facial dysmorphology, and CNS structure and function using an MDT approach. Although all these systems recommend assessing otherwise unexplained prenatal and postnatal growth restriction, the Canadian and derivative guidelines exclude growth as a diagnostic criterion. The diagnostic systems differ in their definitions of PAE, thresholds for individual diagnostic elements, required combination of elements to confirm an FASD diagnosis and diagnostic classifications.

Diagnosis of FASD can be challenging. Confirmation of PAE by biological mothers during a diagnostic assessment of children with suspected FASD is often difficult: the topic is sensitive and recall bias is possible[174]. Additionally, many children live in foster or adoptive care, and obstetric records often lack details about PAE[80]. In these situations, clinicians should seek firsthand witness reports and child protection, justice and medical records. A standardized tool[175–177] should be used, when possible, to record the pattern of alcohol intake, either at an interview with the biological mother or using witness reports or records. A challenge in evaluating facial dysmorphology is the unavailability of suitable lip-philtrum guides and standards for palpebral fissure length (PFL) for many racial and ethnic groups, including Indigenous Australians[178]. PFL is the distance between the endocanthion and exocanthion of the eye (the inner (nasal) and outer points, respectively, where the upper and lower eyelids meet) and may be shortened following PAE. Because some domains of cognitive function cannot be evaluated in infants and young children, confirmation of brain dysfunction in this population may be based on global developmental delay, established using a validated tool[10,167]. FASD are diagnosed with increasing confidence in children aged 6 years and older, who are more cooperative in physical examinations, and in whom facial dysmorphology and neurocognitive function can be assessed with greater reliability using digital photography and standardized psychometric tests.

In the absence of a 'gold standard' for diagnosis of FASD, no diagnostic system may be considered superior. Each system has advantages and disadvantages, including its use in clinical and community settings and the sensitivity and specificity of diagnostic criteria. Diagnosis using these systems shows incomplete agreement[179–181], confirming the need for a unified approach internationally (Table 1 and Supplementary Boxes 1 and 2).

A clinical diagnosis of FASD requires recognition of neurodevelopmental disabilities and a reproducible pattern of minor malformations (dysmorphic features), none of which are pathognomonic, and many of which overlap with other teratogenic or genetic disorders (phenocopies). Thus, a diagnosis of FASD is a diagnosis of exclusion

that is made after considering and excluding other causes for the phenotype[10,167]. For example, prenatal exposure to teratogens, such as toluene, anticonvulsants or phenylalanine (when the mother has phenylketonuria), can result in dysmorphic features also observed in FASD[10,182,183]. Additionally, postnatal exposures (such as adverse childhood experiences (ACE)) can contribute to neurodevelopmental impairment, comorbidities (Box 1) and adverse 'secondary' outcomes (Box 2). Genetic conditions with dysmorphic features similar to FASD include Aarskog syndrome, blepharophimosis, ptosis, epicanthus inversus syndrome, CHARGE syndrome, de Lange syndrome, 22q11.2 deletion, Dubowitz syndrome, inverted duplication 15q, Noonan syndrome, Smith–Lemli–Opitz syndrome and Williams syndrome. Patients with intellectual disability without a recognizable pattern of anomalies may also share some dysmorphic features with FASD[10,182]. Thus, before establishing a diagnosis of FASD, it is important to ask whether the family history suggests a genetic disorder, whether other teratogenic exposures occurred during pregnancy and whether the patient has features not previously described in FASD. If so, referral to a clinical geneticist/dysmorphologist for evaluation is recommended. When indicated, genetic testing should include chromosome microarray analysis[184,185] and exclusion of Fragile X syndrome[186] as a minimum, and whole-exome sequencing should be performed if other genetic pathologies due to point mutations are suspected[10,187]. When PAE is confirmed and/or the physical and neurodevelopmental examinations are supportive, the diagnosis can be made by a paediatrician or other health professional familiar with FASD.

Neurobehavioural impairment accounts for the major functional disabilities associated with FASD. Although the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)[188] criteria for intellectual disability are not always met in patients with FASD, cognitive impairment is often identified and can affect multiple domains, including executive function, memory, mathematical and other academic

Table 1 | Comparison of key diagnostic criteria for the three most commonly used diagnostic systems

Diagnostic categories	Diagnostic criteria						
	Confirmed PAE[a]	Sentinel facial features	Growth deficiency	Structural brain abnormality (OFC)[b]	Structural brain abnormality (brain imaging)[b]	Functional brain abnormality[c]	Other birth defects
Fetal alcohol syndrome							
CoFASP[10] — fetal alcohol syndrome	–	2 of 3[d]	≤Tenth centile	≤Tenth centile[b]	Or[b,e]	≤1.5 SD[f]	–
4-Digit Diagnostic Code[166] — fetal alcohol syndrome	–	3 of 3	≤Tenth centile	≤Third centile[b]	Or[b,g]	Or ≤2 SD[b,h]	–
Canadian[167] — FASD with sentinel facial features	–	3 of 3	–	≤Third centile[i]	Or[b]	≤2 SD[j]	–
Partial fetal alcohol syndrome							
CoFASP[10]	Required	2 of 3	–	–	–	≤1.5 SD	–
CoFASP[10]	–	2 of 3	≤Tenth centile[b]	Or ≤tenth centile[b]	Or[b]	≤1.5 SD[b]	–
4-Digit Diagnostic Code[166]	Required	3 of 3[j]	–	≤Third centile[b]	Or[b,g]	Or ≤2 SD[b]	–
FASD without sentinel facial features							
CoFASP[10] — alcohol-related neurodevelopmental disorder	Required	–	–	–	–	≤1.5 SD	–
CoFASP[10] — alcohol-related birth defects	Required	–	–	–	–	–	Required
4-Digit Diagnostic Code[166] — static encephalopathy, alcohol exposed	Required	–	–	–	Required[k]	Or ≤2 SD[b]	–
4-Digit Diagnostic Code[166] — neurobehavioural disorder, alcohol exposed	Required	–	–	–	–	Moderate	–
Canadian[167] — FASD without sentinel facial features	Required	–	–	–	–	≤2 SD	–

Growth deficiency is defined as prenatal or postnatal height and/or weight ≤tenth centile. –, Criterion not required; CNS, central nervous system; CoFASP, Collaboration on FASD Prevalence; FASD, fetal alcohol spectrum disorder; OFC, occipital frontal circumference; PAE, prenatal alcohol exposure. [a]Requirements for PAE are more stringent in the CoFASP system than the 4-Digit Diagnostic Code or the Canadian Guidelines. [b]Use of the word 'or' indicates that one or the other adjacent element must be present to meet a criterion for diagnosis. [c]Neurological, cognitive or behavioural impairment. [d]Different normative values and cut-offs are used to establish the presence of sentinel facial features among the various diagnostic systems; for example, palpebral fissure length ≤third centile for Canadian Guidelines and 4-Digit Diagnostic Code versus ≤tenth centile for CoFASP. [e]Small OFC, structural brain abnormality or otherwise unexplained recurrent seizures qualify. [f]Or developmental delay if <3 years old. [g]4-Digit Diagnostic Code requires at least one structural or neurologically significant abnormality. Structural abnormalities may include either microcephaly (small OFC) or imaging abnormalities such as hydrocephalus, corpus callosum dysgenesis or heterotopias. [h]4-Digit Diagnostic Code functional impairment ≤2 SD in three or more domains on standardized psychometric tests. [i]Canadian Guidelines include small head circumference in infants and young children but not in older children. [j]Partial FAS in 4-Digit Diagnostic Code includes most but not all of the criteria for growth deficiency and/or facial dysmorphology coupled with severe CNS abnormalities. [k]4-Digit Diagnostic Code diagnosis of static encephalopathy/alcohol exposed requires severe CNS abnormalities (structural, neurological and/or functional abnormalities).

Box 1

Common comorbidities in patients with fetal alcohol spectrum disorders

More than 400 comorbid conditions have been identified in individuals with fetal alcohol spectrum disorders, which span 18 of the 22 chapters of the ICD-10 (ref. [13]), the most prevalent coming from the groups of:

Congenital malformations, deformations and chromosomal abnormalities (Chapter XVII) and Mental and behavioural disorders (Chapter V). Shown below are selected comorbid conditions (with codes) from Chapters V and XVII and diseases of the eye (Chapter VII) and ear (Chapter VIII). For more detailed information, see ref. [13].

Chapter XVII. Congenital malformations, deformations and chromosomal abnormalities

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

Chapter V. Mental and behavioural disorders

F10.2 Mental and behavioural disorders due to use of alcohol, dependence syndrome
F19.2 Mental and behavioural disorders due to the use of multiple drugs and use of other psychoactive substances, dependence syndrome
F41.1/F33.8 Anxiety/depression
F80.1 Expressive language disorder
F80.2 Receptive language disorder
F81.9 Developmental disorder of scholastic skills, unspecified
F89 Unspecified disorder of psychological development
F90.0 Disturbance of activity and attention
F91 Conduct disorder
G40 Epilepsy/seizure disorder

Chapter VII. Diseases of the eye

H47.0 Disorders of optic nerve
H52.6 Refractive errors
H54 Visual impairment
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

Chapter VIII. Diseases of the ear

H65.0 Acute serous otitis media
H65.2 Chronic serous otitis media
H90.8 Mixed conductive and sensorineural hearing loss, unspecified

skills, attention and visuospatial processing[80,189]. Poor social skills, inattention and impaired impulse control can adversely affect school and work performance and independent living.

Although no specific constellation of neurobehavioural deficits have been identified in FASD, some groups have attempted to characterize clusters of impairment associated with PAE[190,191]. One set of criteria, Neurodevelopmental Disorder associated with PAE, has been proposed as a condition for further study in the DSM-5 (ref. [188]); it requires deficits in cognition, behaviour and social adaptation. The ICD-11, published in 2022, lists several 'toxic or drug-related embryofetopathies' (code LD2F.0) including 'fetal alcohol syndrome' (code LD2F.00)[192]. The confounding or potentiating influence of ACE presents a major challenge in identifying a specific neurobehavioural profile[193].

Screening for alcohol use in pregnancy

Early detection of alcohol use during pregnancy can lead to decreased consumption, abstinence or decreased risk of alcohol use in subsequent pregnancies[22,194]. The early identification of alcohol use facilitates education about the harms of PAE, delivery of timely, office-based brief interventions, and referral to substance use treatment services if required. Reducing the high prevalence of FASD requires large-scale, population-based screening programmes to ensure that every pregnant woman is asked about alcohol use, with special attention to populations at high risk[22,195,196] (Table 2).

Screening for alcohol use during pregnancy is underused globally[197,198]. Barriers to screening include lack of public-health guidelines[199] or screening mandates, insufficient clinician training[200–203], competing demands on clinician time, the cost of completing validated alcohol use screening questionnaires[204–206], and the unavailability of clinically reliable biological markers for PAE. Even a single, clinician-directed question about alcohol use may reduce PAE[207,208]; however, successful screening requires that practitioners understand the importance of preventing PAE and providing non-judgmental screening and brief interventions[196]. Preliminary evidence suggests that web-based or app-based mobile health interventions may mitigate patient stigma and reluctance to report alcohol use and might circumvent barriers related to clinician time constraints, training and motivation[209]. Similarly, mobile health approaches may reduce alcohol and substance use in the preconception, prenatal, and postnatal periods[209] and improve access to interventions for families in rural and remote settings. Empathic, compassionate support of abstinence during pregnancy may improve opportunities for treatment of substance use disorders[22,47,196,202]. Screening for alcohol and substance use should be repeated throughout pregnancy and equally across populations to avoid stigmatizing

marginalized populations with selective screening[22,196,210,211]. People who screen positive should be directed to a well-developed management pathway for clinical care.

Prevention

Prevention (Fig. 7) and treatment of alcohol and substance use disorders in pregnancy are central to the 2015 United Nations Sustainable Development Goals (SDG 3.5)[212]. The WHO recommends universal screening and intervention for alcohol use in pregnancy as a primary prevention strategy for FASD[22,213]. Prevention programmes should be evidence based and evaluated following implementation. A wide range of approaches has been deployed, including public awareness strategies, preconception interventions (such as preconception clinics and school-based FASD education), holistic support of women with substance use disorders, and postpartum support for new mothers and babies[214,215]. These approaches show promise in increasing awareness of FASD and decreasing alcohol use during pregnancy[216]; however, the quality of supporting evidence is highly variable. Any primary prevention strategy must be underpinned by evidence-based policy and legislation intended to minimize harms from alcohol, including increased alcohol pricing and taxation, restrictions on advertising and promotion of alcohol, and restricted access to alcohol such as by limiting opening hours and the density of liquor outlets[217]. Public-health authorities agree that the alcohol industry should have no involvement in the development of public-health policies owing to their inherent conflict of interest[218,219]. The framework in Fig. 7 illustrates one approach that could be linked to national policy to address diverse aspects of population-based prevention of FASD.

Level 1: raising public awareness through campaigns and other broad strategies. Public-health initiatives that promote and support women's health, in general, may raise awareness about PAE/FASD. More specific measures include warning signs on alcohol products, pamphlets and public education programmes that encourage healthy, alcohol-free pregnancies[220,221]. However, evidence in support of these campaigns is preliminary[216]. Moreover, campaigns that use triggering imagery or blaming/shaming language (such as 'FASD is 100% preventable') can stigmatize and isolate pregnant women who use alcohol, particularly when paired with judgmental interventions[196]. Reframing alcohol use in pregnancy as a shared responsibility of women, partners, prenatal health-care providers, treatment programmes for substance use disorder, families, community and government may be helpful[222].

Level 2: brief counselling with women and girls of reproductive age. Discussing alcohol use and its associated risks with women of childbearing age during preconception conversations about reproductive health is effective in preventing PAE and FASD[215], primarily by improving contraception use[207]. Screening, Brief Intervention and Referral to Treatment (S-BIRT) for non-pregnant adolescent and adult women reduces the risk of PAE[207], particularly following multi-session interventions[223]. Preliminary studies suggest that such interventions are also beneficial for Indigenous communities[224,225].

Level 3: specialized prenatal support. Treatment for alcohol use during pregnancy may prevent ongoing PAE and decrease adverse infant outcomes[226]. The combination of case management by a social worker or nurse (including problem identification and preparation, implementation and monitoring of a health-care plan) and motivational interviewing (an evidence-based approach to facilitating behaviour change) reduce drinking by pregnant women at high risk[194]. Moreover, specialized, intensive home-visiting interventions for pregnant women at high risk improve maternal and child outcomes and are cost-effective in preventing new cases of FASD[227,228]. Improving maternal nutrition and reducing smoking and family violence may also improve child outcomes in current and future pregnancies[227,229,230].

Level 4: specialized postnatal support. In the postpartum period, home-visiting of women at high risk by health professionals or lay supporters improves child outcomes and reduces the risk of PAE in future pregnancies[227,231,232]. Application of a FASD prevention framework requires consideration of local policy and practices. Best practice programmes support the needs of both the mother and child, recognizing the connections between women's alcohol use, parenting, family influences and child development. Central to the effective implementation of prevention strategies is the establishment of strong cross-cultural and community partnerships and the embrace of cultural knowledge systems and leadership[233]. Mitigating stigma is vital while addressing the structural and systemic factors that promote prenatal alcohol consumption[35].

Management

Principles of management of FASD

The complex pathophysiology of FASD (Boxes 1 and 2) emphasizes the need for thorough, individualized assessment and treatment. Treatment plans should be culturally appropriate, consider

Box 2

Challenges for adolescents and adults with fetal alcohol spectrum disorders

- Involvement in child welfare services (75%)[309]
- Disrupted school experiences due to learning and/or behavioural problems (61%)[267]
- Interaction with the justice system (30%[309] to 60%[267])
- Confinement (detention, prison, or psychiatric or alcohol/drug inpatient setting; 50%)[267]
- Substance use disorder: alcohol and other drugs (50%)[309]
- Inappropriate sexual behaviour (49%)[236,310]
- Increased risk of metabolic abnormalities (includes type 2 diabetes, low high-density lipoprotein, high triglycerides, and female-specific overweight and obesity)[311]
- Difficulties with independent living and trouble gaining and retaining employment (80%)[267]
- Mean life expectancy (34 years; 95% CI 31–37 years) is considerably lower than in the general population[275]; leading causes of death are 'external causes' (44%), including suicide (15%), accidents (14%), poisoning by illegal drugs or alcohol (7%) and other external causes (7%)

the family and community context, and be developed in partnership with families and individuals with lived experience of FASD[234,235].

Therapeutic approaches must be tailored to individual strengths and needs. For example, an individual who has experienced trauma but has normal intelligence and social and emotional skills requires a trauma-informed, emotion-focused approach. By contrast, an individual with cognitive deficits and poor social and emotional skills may require a more directed, psycho-educational approach or environmental modifications to support and prevent secondary outcomes of FASD such as poor academic performance or inability to obtain/maintain employment[236].

Management involves multiple service providers and changing interventions across the lifespan. Treatment comprises interventions to anticipate the delivery of a newborn with PAE, prevention of exposure to ACE, home-visiting by a public-health nurse, referral to infant developmental services, vision and hearing screening, preschool speech and language therapy, school-based support for learning disorders, occupational and physical therapy, behavioural and psychological interventions, pharmacotherapy, vocational support, and support for independent living in adolescence and adulthood. Specialized medical or surgical interventions may be required for congenital anomalies and accompanying comorbidities. There remains limited evidence from high-quality trials to support specific interventions for FASD[237,238].

Behaviour support. Several large-scale randomized controlled trials (RCTs) support specific developmental and psychological interventions for FASD in children but few high-quality studies have been conducted in adolescents and adults[237].

Positive behaviour support[239] is supported by positive results from RCTs and underpins three interventions for FASD: GoFAR[240], the Math Interactive Learning Experience (MILE)[241] and the Families Moving Forward programme[242]. Positive behaviour support strengthens skills that enhance success and satisfaction in social, academic, work and community settings while proactively preventing problem behaviours; maintaining family involvement is an important element[16]. Where available, these specialized programmes oblige therapists to prioritize treatment for individuals most likely to benefit. The GoFAR intervention (FAR is an acronym for Focus and plan, Act, and Reflect) promotes self-regulation and adaptive function using direct instruction, practice and feedback, and strategies for emotional and behavioural self-regulation[243]. Interventions such as GoFAR, which involve the child and parents in the context of real-life adaptive behavioural problems, improve daily living skills and attention[243]. The MILE intervention provides individualized mathematical instruction through interactive learning and environmental modifications and improves math knowledge and parent report of child behaviour problems[241,244,245]. Families Moving Forward helps parents reframe their child's behaviour within a neurodevelopmental paradigm. Adaptation of this approach to an app-based platform may reduce barriers to care[242].

Self-regulation and executive function. Most children with FASD have significant problems with executive function and self-regulation[189]. The ALERT programme, a 12-week manualized approach using sensory integration and cognitive behavioural strategies, aims to help children regulate their behaviour and address sensory challenges[246] in a home environment[247,248] but is less effective when delivered in schools[249].

Table 2 | Alcohol use screening instruments for pregnant women (all ages)

Screening tool	Items (*N*)	Focus	Formats	Sensitivity (%)[a]	Specificity (%)[a]
Alcohol only					
T-ACE	4	Risky drinking	Clinician directed; paper-based questionnaire	69–100	19–89
TWEAK	7	Risky drinking	Clinician directed; paper-based questionnaire	59–100	36–83
AUDIT-C	3	Alcohol use frequency, amount and 'binge' episodes; risk score	Clinician directed; paper-based questionnaire	18–100	71–100
AUDIT	10	Alcohol use frequency, amount and 'binge' episodes; risk score	Clinician directed; paper-based questionnaire	7–87	86–100
CAGE	4	Risky drinking	Paper-based questionnaire	38–59	82–93
SMAST	13	Risky drinking	Paper-based questionnaire	7.5–15	96–98
TQDH	10	Alcohol use	Clinician directed	NA	NA
NET	3	Risky drinking	Paper-based questionnaire	24–71	86–99
1-Question screen	1	Timing of last drink	Clinician directed	97	98
Alcohol and other substances					
4P's Plus	5	Any alcohol/tobacco use (past/pregnancy); risky drinking in partner, parents	Paper-based questionnaire	87–90	30–76
ASSIST	8	Any substance use; problematic use	Clinician-directed interview	67	36
SURP-P	3	Any substance use; problematic use	Paper-based questionnaire	48–65	68–85
HSQ	18–40	Any substance use	Paper-based questionnaire	NA	NA
PIP	~200	Any substance use	Computer-based questionnaire	NA	NA

ASSIST, Alcohol, Smoking and Substance Involvement Screening Test; AUDIT, Alcohol Use Disorders Identification Test; CAGE, Cut down, Annoyed, Guilty, Eye-opener; HSQ, Hospital Screening Questionnaire; NA, not assessed; NET, Normal drinker, Eye-opener, Tolerance; PIP, Pregnancy Information Program; SMAST, Short Michigan Alcohol Screening Test; SURP-P, Substance Use Risk Profile in Pregnancy; T-ACE, Tolerance, Annoyance, Cut Down, Eye-opener; TQDH, Ten Question Drinking History; TWEAK, Tolerance, Worried, Eye-opener, Amnesia, K/Cut Down. [a]Refers to detection rates of alcohol use in pregnant women, when available, at the traditional cut-off points. Reprinted from ref. [196], Springer Nature Limited.

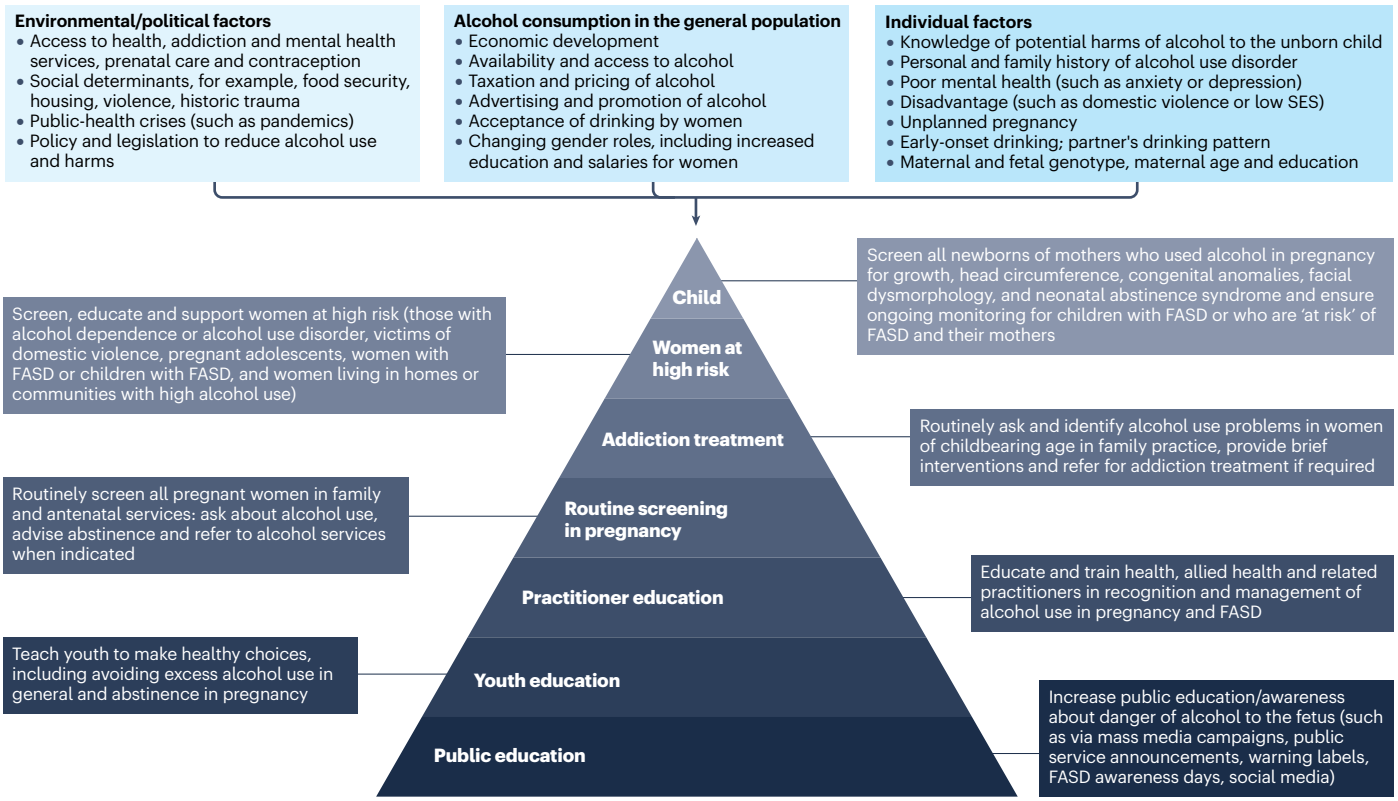

Fig. 7 | Cultural, socioeconomic and environmental factors influencing alcohol use in pregnancy and strategies for prevention of FASD. A hierarchy of strategies can be used to prevent fetal alcohol spectrum disorder (FASD), ranging from awareness campaigns for the whole population to health, educational and social support for women and children. The strategies are placed in the context of cultural, political and environmental factors that influence access to, use of and attitudes towards alcohol use in pregnant women. SES, socioeconomic status.

ALERT programme training is available online but requires adaptation to the family and community context[249].

Social skills. Interventions to improve social connections in children with FASD include the Children's Friendship Training (CFT)[250] and the Families on Track programme[251]. CFT involves 12 weeks of social and friendship skill training for children with FASD and their parents; it improves social skills and decreases problem behaviours in children with FASD[250]. Similarly, the Families on Track programme increases emotional regulation and self-esteem and decreases anxiety and disruptive behaviour[251]. However, interventions such as CFT and Families on Track are not widely available, and barriers to their use include the need to adapt to cultural context[252]. International partnerships and sharing of expertise may increase accessibility to these interventions[252].

Pharmacological interventions

Pharmacological interventions for FASD are widely used and include medications, such as cognitive enhancers, to treat core impairments and medications to treat comorbidities, including ADHD, anxiety, and arousal or sleep disorders[253]. Large RCTs evaluating their effectiveness in FASD are urgently needed.

Children with FASD and ADHD have a different pattern of neurocognitive and behavioural abnormalities than children with ADHD alone[254], suggesting the need for a tailored therapeutic approach. Expert consensus approaches for the management of ADHD in FASD have been developed. Recommendations in the UK suggest the use of a dexamphetamine-based medication (rather than a methylphenidate-based medicine) for first-line treatment of ADHD in children and adults with FASD; however, research is needed to understand the basis of treatment responses[255]. Guanfacine XL or similar medications can be used in individuals with comorbidities such as autism spectrum disorders[255]. Algorithms have also been developed in Canada for the use of psychotropic medications in FASD[256]. Although based on clinical consensus, these strategies form the basis for future research[256].

Preclinical trials suggest that choline supplements improve cognitive deficits following PAE but clinical data are limited[257]. A small, placebo-controlled RCT demonstrated that children who received choline supplementation had higher non-verbal intelligence and visual-spatial skills, better working memory and verbal memory, and fewer behavioural symptoms of ADHD at 4-year follow-up than children who received placebo[258]. Despite these positive results, choline supplementation is not routinely recommended for children with FASD due to a lack of strong evidence for its effectiveness.

The role of exposure to adversity

A relationship between PAE and ACE is well established, and both may influence the life course in FASD[193]. Comprehensive neuropsychological assessment and MRI show that PAE accounts for the largest

proportion of the variance in regional brain size and brain function in children with both exposures[259]. Furthermore, PAE imparts more risk for adverse outcomes than ACE in individuals with PAE in adoptive care[260]. However, adversity does affect the developmental trajectory and ACE are associated with maladaptive problems in children with FASD[261]. For example, school-age children with FASD and ACE are particularly vulnerable to language and social communication deficits[262], which are hypothesized to result from the additive effect of prenatal and postnatal environmental exposures. This emphasizes the need for an individualized approach to treatment for individuals with life trauma and FASD.

Attempts have been made to understand the individual and combined effects of PAE and postnatal events on individual behaviours in FASD[263]. One model of complex trauma (Supplementary Fig. 1) displays neurodevelopmental variation as a complex interplay between prenatal and postnatal events and improves understanding of their interactions and association with outcomes. Child maltreatment viewed through a neurodevelopmental lens highlights the benefit of a sequential model of therapeutics rather than a focus on specific therapeutic techniques[264].

Supplementary Fig. 1 highlights how vulnerabilities may present, whereas Supplementary Fig. 2 identifies methods to manage the same vulnerabilities based on understanding the individual and using anticipatory interventions to support development. Box 3 contains some useful resources on FASD for professionals and parents.

Box 3

Resources on alcohol use in pregnancy and fetal alcohol spectrum disorders

- Australian guidelines to reduce health risks from drinking alcohol
- Canada No. 245 — Alcohol Use and Pregnancy Consensus Clinical Guidelines[312]
- Centers for Disease Control and Prevention
- Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD)
- Fetal Alcohol Spectrum Disorders (FASD) — American Academy of Pediatrics
- FASD Hub Australia
- FASD United
- FAS-UK
- FASD — Care Action Network
- Learning with FASD
- National Organization for FASD Australia (NOFASD)
- National Institute for Health and Care Excellence UK. Quality Standard QS204. FASD
- National Institute on Alcohol Abuse and Alcoholism. Fetal Alcohol Exposure
- Pan American Health Organization. Assessment of Fetal Alcohol Spectrum Disorders (2020)[313]
- The European FASD Alliance
- WHO. Guidelines for identification and management of substance use and substance use disorders in pregnancy (2014)[22]

Quality of life

Few published studies address QOL in individuals with FASD. One systematic review and meta-analysis identified more than 400 comorbid conditions among individuals with FASD, spanning 18 of 22 chapters of the ICD-10 (ref. [13]). The most prevalent conditions were within the chapters of "Congenital malformations, deformations, and chromosomal abnormalities" (Chapters Q00–Q99; 43%) and "Mental and behavioural disorders" (Chapters F00–F99; 18%). Comorbid conditions with the highest pooled prevalence (50–91%) included abnormal functional studies of the peripheral nervous system and special senses, conduct disorder, receptive and expressive language disorders, and chronic serous otitis media[13]. Other studies report a high prevalence of vision and hearing problems among people with FASD[265,266]. All of these comorbid conditions affect the function and QOL of individuals with FASD and their families (Box 1).

Neurodevelopmental impairments may lead to lifelong 'secondary' disabilities, including academic failure, substance abuse, mental health problems, contact with law enforcement and inability to live independently or obtain/maintain employment[267] (Box 2). These conditions adversely affect QOL and require health, remedial education and correctional, mental health, social, child protection, developmental, vocational and disability services across the lifespan[17,268,269]. Lack of societal understanding of FASD is a barrier to addressing these secondary disabilities[16,270].

A shift from a deficit-based to a strength-based management approach emphasizes the need to harness the abilities of individuals with FASD to improve their QOL and well-being. A review of 19 studies exploring the lived experience of people with FASD highlighted their strengths, including self-awareness, receptiveness to support, capacity for human connection, perseverance and hope for the future[271]. The lack of accessible, FASD-informed services perpetuates a deficit-based model.

Longitudinal cohort studies of FASD consistently show that adverse outcomes are more likely where support services are lacking. These studies are limited by selection bias and are based on cohorts with severe deficits rather than population-based cohorts receiving adequate support[267,270]. Nevertheless, they suggest the potential to modify developmental trajectories by addressing postnatal environmental exposures and opportunities. To address QOL, future studies should better articulate outcomes of interest for individuals and families living with FASD[272].

Mortality

FASD is associated with an increased risk of premature death of affected individuals, their siblings and mothers[273,274]. One study reported a mean age at death of 34 years for individuals with FASD[275]. Individuals with FASD have nearly fivefold higher mortality risk than people of the same age and year of death, and nearly half of all deaths occur in young adults[276]. In childhood, the leading causes of death in FASD are congenital malformations of the CNS, heart or kidney, sepsis, cancer, and sudden infant death syndrome, and more than half of deaths (54%) occur in the first year of life[277]. In the USA, >29% of adolescent males with FASD reported a serious suicide attempt, which is >19-fold higher than the national average[236,278].

Among children and adolescents with FASD, the mortality rate of siblings with and without FASD is 114 per 1,000, which is approximately

sixfold higher than among age-matched controls[273]. Furthermore, mothers of children with FASD have a 44.8-fold increased mortality risk compared with mothers of children without FASD[274].

Caregiver burden

The complexity of parenting a child with FASD increases across adolescence and young adulthood. Caregivers of children with FASD experience increased burden, levels of stress and feelings of isolation[279,280]. The lifelong challenges and unmet needs of caregivers negatively affect family functioning and QOL[281].

Early recognition of FASD and early emphasis on the prevention of secondary disabilities may decrease demands on families. Moreover, a diagnosis of FASD may indicate the need for specific interventions and parenting supports such as respite care, peer-support groups, treatment for parental alcohol misuse and education of other professionals who care for people with FASD.

Outlook

FASD are the most common preventable cause of neurodevelopmental impairment and congenital anomalies[164]. These disorders are the legacy of readily available alcohol and societal tolerance to its widespread use, including during pregnancy. FASD affect all strata of society, with enormous personal, social and economic effects across the lifespan.

Diagnostic challenges

The greatest global challenges in the clinical management of FASD are the paucity of resources for diagnosis and treatment and the large number of affected individuals[163]. A substantial increase in resources is required, both for centres of expertise with MDTs and to build diagnostic capacity among non-specialist health services. However, this alone will not bridge the gap in services for children and adults, and a paradigm shift is needed. This might include recognition of the important role of primary care providers and use of new technologies such as app-based screening, diagnostic and treatment tools. Telehealth services will reduce the need for face-to-face care[282] and tele-education could build clinician awareness and skills, especially in rural and remote areas[283]. However, in many low-income and middle-income countries, this technology is not widely available.

Without a definitive diagnostic test, a clinical diagnosis of FASD must be made. Diagnosis is facilitated by identification of PAE in association with neurodevelopmental impairment, with or without specific craniofacial dysmorphology, and exclusion of alternative diagnoses. Many clinicians fail to document alcohol use in pregnancy or PAE in children, highlighting the need for enhanced training, standardized tools to document PAE and, especially, routine screening for alcohol use before and during pregnancy. Biomarkers for PAE are urgently needed because many children with FASD live in out-of-home care and reliable PAE histories are frequently unavailable. Although biomarkers for PAE (such as fatty acid ethyl esters, ethyl glucuronide and phosphatidylethanol) are identifiable in maternal hair, blood and meconium, their clinical use is limited, and testing may be costly or unavailable[284]. Identification of miRNAs from women in the second trimester and epigenetic signatures in placental and infant tissue hold promise as biomarkers for PAE and hence for risk of abnormal neurodevelopment[154–156,187]; however, further research is required before their use becomes routine in clinical practice[81,125].

Accessible e-health technologies to facilitate the diagnosis of FASD are under development. For example, 3D facial imaging may facilitate diagnosis by automatically quantifying the three sentinel facial features of FASD and identifying more subtle facial dysmorphology that reflects PAE after gastrulation[67,285]. The use and availability of 3D imaging will increase as more sophisticated and cheaper 3D cameras evolve and image capture on smartphones combined with cloud-based image analysis become available. Similarly, web-based tools are in development for identification of neurocognitive impairments associated with FASD. BRAIN-online enables screening for cognitive and behavioural features of PAE or FASD[286]. Decision trees simplify neurocognitive testing by including only tests that contribute most to the diagnosis of FASD[287]. Porting this software to tablets or online websites will broaden access to relevant neurocognitive testing. For example, the FASD-Tree[288] provides a dichotomous indication and a risk score for FASD, considering both neurobehaviour and dysmorphology, and successfully discriminates between children with and without PAE with a high predictive value[289].

The lack of internationally agreed diagnostic criteria for FASD is challenging and hinders the comparison of prevalence and clinical outcomes between studies. In response, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has convened an international consensus committee to analyse data derived from existing diagnostic systems and develop a consensus research classification for FASD[290]. The field would also benefit from improved, population-based, normative data for growth and PFL as well as internationally accepted definitions of a standard drink and of the 'low, moderate and high' levels of risk of PAE. Additionally, the range and aetiology of adult outcomes require clarification to inform assessment and prognosis in FASD[291]. A research initiative for elderly people with FASD is urgently needed as there is virtually no information about the diagnostic criteria or neuropsychological outcomes of FASD in this age group.

Understanding pathophysiology

Functional MRI can be used to elucidate brain growth trajectories and disruptions to neuronal pathways after PAE (including low-level PAE), thereby assisting our understanding of CNS dysfunction in FASD[68]. Advances in our understanding of the genetics of rare neurodevelopmental disorders may identify genes that govern susceptibility or resilience to PAE and provide additional insights into the pathogenesis of FASD[187]. Advances in neuroscience research, including novel preclinical studies, may help elucidate the relationship between PAE-induced brain dysfunction and the FASD phenotype and inform therapeutics and prevention[292].

Prevention and management

Preclinical studies suggest that epigenetic changes induced by PAE underpin metabolic, immunological, renal and cardiac disorders in FASD[13], but further studies in patients are required to confirm this. The paucity of high-quality evidence to inform the treatment of neurodevelopmental impairments and comorbidities associated with FASD across the lifespan requires urgent redress[237,238]. Behavioural, family-based, school-based and pharmacological treatments require evaluation through multicentre RCTs. Moreover, little attention has been paid to preventing and managing the secondary outcomes of FASD in adults: substance use, mental health disorders, contact with the justice system, and issues with sleep, sexuality and violence. These must be prioritized to improve the QOL of individuals and reduce the societal and economic effects of FASD.

The COVID-19 pandemic demonstrated the use of telemedicine for virtual neuropsychiatric assessment and delivery of therapy[282]. Telemedicine approaches may also partly fill the need to increase

health professionals' capacity for FASD-informed care and to help education, child protection and justice professionals to recognize and understand FASD[283].

Improving the primary prevention of alcohol use in pregnancy and hence FASD is also warranted[237,238]. Alcohol consumption and binge drinking are increasing among women of childbearing age in many countries, particularly in the most populous countries such as China and India[26]. This rise reflects increased availability of alcohol, societal acceptance of drinking among women, shifting gender roles, increasing income of women, and targeted marketing of alcohol to women and predicts a future global increase in FASD prevalence. Alcohol use in adolescence predicts subsequent use during pregnancy, and family physicians can play a role in identifying young women at risk[293].

Another concern is that a large proportion of pregnancies globally are unplanned[29], which can result in unintentional exposure of the embryo to PAE in the earliest stages of pregnancy. Accordingly, effective and cost-effective population-based preventive strategies should be adapted such as those promoted by the WHO in their Global Action Plan for the Prevention and Control of NCDs[294] and their Global Strategy to Reduce the Harmful Use of Alcohol[295].

Although the role of national guidelines, community education and family support is important, these efforts must be underpinned by strategies proven to drive behavioural change and reduce alcohol harm, including legislated restrictions on the advertising and promotion of alcohol, appropriate taxation and pricing, and limited access to alcohol through restricted liquor outlets and opening hours and community-initiated alcohol restrictions[26,295].

In pregnant women with ongoing alcohol consumption, food supplementation with folic acid, selenium, DHA, L-glutamine, boric acid or choline may reduce the effects of PAE[87,296]. However, research is required to define optimal levels of nutritional supplementation for pregnancy. Women who consume large amounts of alcohol often have iron deficiency, which increases the risk of FASD, and iron supplementation may be valuable[297]. Although novel in utero therapies with potential to prevent harm from PAE have been explored in preclinical models, none have been proven safe or effective in human RCTs[298–307]. Candidate therapies include agents that reduce ethanol-induced oxidative stress, cerebral neuronal apoptosis, growth deficits and structural anomalies caused by PAE[308].

Future research should be collaborative and informed by people living with FASD and their families. FASD is a lifelong condition and information must be sought about adult patients, including the elderly. Further understanding of the pathophysiology underpinning the teratogenic and neurotoxic effects of PAE is required to inform prevention and management. Moreover, novel diagnostic tools and treatments must be rigorously tested, and new approaches are needed to reduce stigma, improve the QOL of people with FASD and prevent FASD in future generations.

Published online: 23 February 2023

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Acknowledgements

M.E.C. and E.P.R.: part of the work on mechanisms of alcohol harm was done in conjunction with the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), which is funded by grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Support was provided by U24 AA014811 (E.P.R. and M.E.C.). Additional information about CIFASD, including information on how to request data, can be found at www.cifasd.org. H.E.H.: the section on diagnostic guidelines was partially supported by the National Institute on Alcohol Abuse and Alcoholism grants R01 AA11685, R01/U01 AA01115134, and U01 AA019879-01/NIH-NIAAA (Collaboration on Fetal Alcohol Spectrum Disorders Prevalence (CoFASP)), and by the Oxnard Foundation, Newport Beach, CA, USA. E.J.E. is supported by an Australian Medical Research Futures Fund Next Generation Fellowship (#MRF1135959) and National Health and Medical Research Council of Australia funding for a Centre of Research Excellence in FASD (#GNT1110341).

Author contributions

Introduction (E.P.R. and E.J.E.); Epidemiology (S.P.); Mechanisms/pathophysiology (M.E.C.); Diagnosis, screening and prevention (E.J.E., M.E.C., H.E.H., E.P.R., S.P., A.C. and L.B.); Management (R.A.S.M., A.C. and E.J.E.); Quality of life (S.P., L.B. and R.A.S.M.); Outlook (E.J.E. and M.E.C.); Overview of Primer (S.P. and E.J.E.).

Competing interests

The authors declare no competing interests

Informed consent

The authors affirm that human research participants provided informed consent, for publication of the images in Figure 4.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41572-023-00420-x.

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Peer review information *Nature Reviews Disease Primers* thanks C. Chambers, O. Garcia-Algar, J. Kable, C. Valenzuela and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.