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Review Article

Diagnosis of fetal alcohol spectrum disorders: German guideline version 2024

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1. Introduction

Fetal alcohol spectrum disorder (FASD) is a generic term for disorders resulting from prenatal exposure to alcohol. This includes fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorders (ARND) and alcohol related birth defects (ARBD). FASD is a complex disorder that has a significant negative impact on the daily functioning and quality of life of the affected child and their caregivers.

According to the results of the GEDA survey (Gesundheit in Deutschland Aktuell) conducted by the Robert Koch Institute in 2012 [1], a total of around 28 % of pregnant women reported alcohol consumption. Of these, approx. 20 % showed moderate and approx. 8 % risky consumption (according to the AUDIT-C questionnaire). No amount of prenatal alcohol exposure (PAE) is considered completely safe for the child's development [2]. Binge drinking (at least 5 standard drinks on one occasion) was reported by approx. 12 % of pregnant women less than once a month, about 4 % every month and about 0.1 % at least once a week. These high figures show that alcohol consumption during pregnancy is not an isolated problem, but a social and health policy issue.

The estimated prevalence of FASD varies greatly depending on the country. The World Health Organisation (WHO) European Region has the highest prevalence, with a rate of 1.98 % [3]. In Germany, statistical estimates by Kraus et al. (2019) indicate that the incidence of FASD is 177 children per 10,000 live births [4]. This makes FASD one of the most common 'congenital' chronic neurological diseases. As there is no gold standard for diagnosing FASD, these prevalence estimates are constrained by variations in diagnostic practices and methodologies. Although these figures offer valuable insights, they underscore the necessity for standardized diagnostic criteria to enhance the detection and management of FASD globally.

FASD is not curable, but an early, correct diagnosis and a stable, supportive environment are positive factors for the long-term prognosis of the respective symptoms [5,6].

The German guideline presented here provides evidence-based, clinically relevant and easy-to-use diagnostic criteria and recommendations for the identification of FASD in children and adolescents (0–18 years of age).

As the first guideline development in Germany in 2012 showed [7,8], guidelines increase the awareness of professionals regarding FASD and represent a step towards improving the detection and care of children with these disorders.

2. Methods

In 2022, a guideline consensus group was established, including representatives of 15 German professional societies, 10 FASD-experts and 2 members of the patient support group "FASD Deutschland". The consensus process was accompanied by methodological supervisors also facilitating the consensus process (Table 1). Additionally, two non-voting observers of the German Ministry of Health attended the conferences (Manuela Schumann, Kirsten Reinhard MD).

All members of the consensus group provided a declaration of interest according to international requirements [9]. All declarations were evaluated by an independent conflict of interest officer and discussed at the first guideline conference. None of the members of the consensus group had conflicts of interest that would have required them to be excluded from the voting process or parts thereof. To counteract unwarranted influences to the guideline content by individual interests, a balanced composition of the guideline group and a structured approach to reach consensus for recommendations, facilitated by an independent moderator were established.

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Table 1
Members of the guideline-consensus-group.

Guideline coordinators - Institutions	Names
Ludwig-Maximilians-University of Munich (LMU), Department of Neuropaediatrics, Social Paediatric Centre	Prof. Mirjam Landgraf MD
Ludwig-Maximilians-University of Munich (LMU), Department of Neuropaediatrics, Social Paediatric Centre	Sonja Strieker
Ludwig-Maximilians-University of Munich (LMU), Department of Neuropaediatrics, Social Paediatric Centre	Prof. Florian Heinen MD
Institute for Evidence in Medicine (IFEM), University of Freiburg	Christine Schmucker MD
Institute for Evidence in Medicine (IFEM), University of Freiburg	Annika Ziegler
Methodological supervision: Association of the Scientific Medical Societies in Germany (AWMF)	**Representatives**
AWMF-Institute for Medical Knowledge Management, Philipps-University, Marburg	Prof. Ina Kopp MD (Director) Monika Nothacker MD (Vice Director)
German Scientific Societies and Professional Associations	**Representatives**
Society of Neuropaediatrics (Germany, Austria, Switzerland) (GNP)	Prof. Mirjam Landgraf MD
German Society of Paediatrics and Adolescent Medicine (DGKJ)	Prof. Florian Heinen MD
German Society of Social Paediatrics and Adolescent Medicine (DGSPJ)	Juliane Spiegler MD
German Society of Gynaecology and Obstetrics (DGGG)	Dietmar Schlembach MD
German Society for Prenatal and Obstetric Medicine (DGPGM)	
German Society of Neonatology and Paediatric Intensive Care (GNPI)	Prof. Rolf F. Maier MD
German Society for Perinatal Medicine (DGPM)	Silvia Lobmaier MD
German Society of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP)	Prof. Christine Freitag MD Substitution: Prof. Frank Häßler MD
German Society of Addiction Research and Addiction Treatment (DG Sucht)	Prof. Bernd Lenz MD
German Society of Addiction Psychology (dg sps)	Prof. Tanja Hoff
German Society of Addiction Medicine (DGS)	Prof. Ulrich Preuss MD Substitution: Prof. Markus Backmund MD
German Association of Midwives (DHV)	Andrea Köbke
Professional Association of Paediatricians (BVKJ)	Matthias Brockstedt MD
Professional Association of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (BKJPP)	Annegret Brauer MD
Federal Association of Physicians of the Public Health Services (BVÖGD)	Gabriele Trost-Brinkhues MD
Professional Association of German Psychologists (BDP)	Ralph Schliewenz Substitution: Johanna Thünker
FASD Experts	**Names**
Former professor of FASD Centre at Charité University, Berlin	Prof. Hans-Ludwig Spohr
Social Paediatric Centre of Charité University, Berlin	Heike Wolter
Director of the children's home and FASD Centre Sonnenhof, Berlin	Gela Becker Lina Schwerg
Director of the Social Paediatric Centre St. Georg, Leipzig	Heike Hoff-Emden MD
FASD Centre, University of Münster	Reinhold Feldmann
FASD Centre at the Social Paediatric Centre at Hospital Ludmillenstift, Meppen	Dorothee Veer MD
Social Paediatric Centre at the Carl-Thiem-Hospital, Cottbus	Kristina Kölzsch MD
FASD Centre for Adults at Elisabeth-Herzberge-Hospital, Berlin	Björn Kruse MD Jessica Wagner
Director of the German Association of the Scientific Medical Societies (AWMF-IMWi)	Prof. Ina Kopp MD (non-voting)
Child and Adolescent Psychiatry hospital, kbo Heckscher Hospital, Munich	Anna Hutzelmeyer-Nickels MD
Advocate for Child and Adolescent Rights, specialised in FASD	Gila Schindler
German Patient Support Group FASD Deutschland e.V.	**Representatives**
President of the Patient Support Group FASD Germany	Gisela Michalowski Substitution: Katrin Lepke
Board Member of the Patient Support Group FASD Germany	Sandra Kramme

influence the development and content of the guideline in any way.

Systematic retrieval of the literature and determination of levels of evidence were conducted by the Institute for Evidence in Medicine (IFEM) at the University of Freiburg in consultation with the guideline coordinators at the LMU University of Munich. The AWMF (Association of the Scientific Medical Societies in Germany) provided methodological guidance and facilitation of consensus processes.

The key question (based on the PICOS scheme: population, intervention, controls, outcome, study design) for the systematic literature review was:

Which development-related criteria (I) in childhood and adolescence (0–18 years of age) (P):

- enable the diagnosis of FAS, pFAS, ARND and ARBD as part of FASD (O)

and/or

- are associated with positive outcomes in FAS, pFAS, ARND and ARBD belonging to FASD (O)?

ePub Table 1 shows the items of the different categories of PICOS scheme representing the inclusion criteria, as well as the exclusion criteria for the systematic literature search. In contrast to other guidelines, not only systematic reviews were included, but also original studies, as the overall evidence in the field of FASD was estimated as moderate to low in advance. Studies with very low methodological quality had to be excluded to avoid inaccurate data for the guideline development. Animal studies and in-vitro studies were excluded, as they do not directly address human clinical outcomes and may not accurately reflect the complexity in humans regarding the diagnosis of FASD.

The searches were conducted in the bibliographic databases Medline, Cochrane Library, PsycINFO/PsycARTICLES/PSYNDEX (via EBSCO), TRIP Database, Epistemonikos, and included English and German literature. The search strategy for each database is shown in ePub Table 2.

Because this guideline is an update of an existing one (for the former guideline see Refs. [7,8]), the search for primary literature was limited to the period from 1 July 2015 (last search) to 6 July 2022, while no time limit was set for the additional search for international guidelines. In addition, the reference lists of reviews and guidelines identified were screened for further potentially relevant studies.

Full-text publications included in the evaluation were graded according to the levels of evidence provided by the Oxford Evidence Classification System 2011 (ePub Table 3).

According to the level of evidence (from LoE 1 to LoE 5), grades of recommendation were assigned (strong recommendation A "we recommend", weak recommendation B "we suggest", open recommendation 0 "may be considered"), taking into account clinical relevance of outcomes and effect estimates, balance of benefit and harm of diagnostic interventions, practicality of the diagnostic criteria, and ethical considerations. In areas where evidence is limited, expert consensus was formulated based on clinical experience and best practices. Guided by an independent methodologically experienced moderator (Prof. Ina Kopp MD), formal consensus was reached using the Nominal Group Technique [10] at two interdisciplinary consensus meetings (2023).

Table 2
Key recommendations for the diagnosis of fetal alcohol syndrome (FAS).

Diagnostic recommendations	Level of Evidence	Grade of Recommendation[a]	Related literature
First Key Recommendation FAS For the diagnosis of FAS **all criteria 1 to 4** should be present: 1. Growth deficits 2. Facial characteristics 3. Abnormalities of the central nervous system (CNS) 4. Prenatal alcohol exposure: confirmed, probable or unconfirmed	**EC**		
Second Key Recommendation FAS To fulfil the criterion "**Growth deficits**" at least one of the following abnormalities, adapted to gestational age, age and gender, documented at any time, should be present: a. Birth weight or body weight ≤10th percentile b. Birth length or body length ≤10th percentile c. Body Mass Index ≤10th percentile	**2 to 4**	**A**	[11–18]
Third Key Recommendation FAS To fulfil the criterion "**Facial characteristics**" all three facial abnormalities should be present (documented at any time): a. Short palpebral fissure length (at least 2 SD below the mean/≤ 3rd percentile) b. Smooth philtrum (Rank 4 or 5 Lip-Philtrum-Guide) c. Thin upper lip (Rank 4 or 5 Lip-Philtrum-Guide)	**1b- to 4**	**A**	[15,19–35]
Fourth Key Recommendation FAS To fulfil the criterion "**Abnormalities of the central nervous system**" (CNS) at least one of the following anomalies should be found: • Functional abnormalities of the CNS • Structural abnormalities of the CNS	**EC**		
Fifth Key Recommendation FAS To fulfil the criterion "**Functional CNS abnormalities**" at least one of the following deficits, that is not adequate for age and that cannot be explained solely by the familial background or social environment should be found: a. Global intellectual deficit at least 2 SD below the mean (IQ < 70) or significant combined developmental delay of children under the age of two years (if measurable by a standardized test at least 2 SD below the mean) b. Performance at least 2 SD below the mean in at least 3 of the following domains or in at least 2 of the following domains combined with epilepsy: Language/Speech Fine motor functions or coordination Spatial-visual perception or spatial-constructive skills Arithmetic skills Learning or memory skills Executive functions Attention Social skills and behaviour	**2c to 4**	**B**	[36–75]
Sixth Key Recommendation FAS To fulfil the criterion "**Structural CNS abnormalities**" At least one of the following anomalies adapted to gestational age, age and gender, documented at any time, should be found: a. Microcephaly ≤10th percentile b. Structural CNS malformation (global or regional)	**2 to 4**	**B**	[12,15,22,23,25,26,53,73,74,76–106]
Seventh Key Recommendation FAS If there are abnormalities in the three other diagnostic fields (growth, face, CNS) the **diagnosis of FAS should be made even if prenatal alcohol exposure is unknown**.	**3 to 4**	**A**	[77,107–109]

[a] Grades of recommendation: A - strong recommendation: "we recommend"; B - recommendation: "we suggest"; 0 - open recommendation "may be considered".

3. Results

The systematic search in the bibliographic databases resulted in 1847 hits. After application of the inclusion and exclusion criteria (ePub Table 1) 65 full text publications were included in the assessment of evidence (Fig. 1).

The formal consensus process based on the evidence-assessed literature led to seven key recommendations for the diagnosis of FAS (Table 2), four key recommendations for the diagnosis of pFAS (Table 3), and three key recommendations for the diagnosis of ARND (Table 4).

All recommendations were adopted with "strong consensus" (agreement by > 95 % of the participating guideline group members) or "consensus" (agreement by > 75 % of the participating guideline group members).

Additionally, background information and recommendations for the assessment of the key diagnostic criteria are given.

EC - expert consensus.

Table 3
Key recommendations for the diagnosis of partial fetal alcohol syndrome (pFAS).

Diagnostic recommendations	Level of Evidence	Grade of Recommendation	Related literature
First Key Recommendation pFAS For the diagnosis of pFAS **all criteria 1 to 3** should be present: 1. Facial characteristics 2. Abnormalities of the central nervous system (CNS) 3. Prenatal alcohol exposure: confirmed or probable	**EC**		
Second Key Recommendation pFAS To fulfil the criterion "**Facial characteristics**" at least two of the following three facial abnormalities should be present (documented at any time): a. Short palpebral fissure length (at least 2 SD below the mean/≤ 3rd percentile) b. Smooth philtrum (Rank 4 or 5 Lip-Philtrum-Guide) c. Thin upper lip (Rank 4 or 5 Lip-Philtrum-Guide)	**1b- to 4**	**A**	[15,19–25, 27–35,76,110]
Third Key Recommendation pFAS To fulfil the criterion **"CNS abnormalities**" at least three of the following deficits, that are not adequate for age and that cannot be explained solely by the familial background or social environment should be found (all bullet points equal): • Global intellectual deficit at least two standard deviations below the mean or significant combined developmental delay of children ≤2 years • Epilepsy • Microcephaly ≤10. Percentile or structural CNS malformation (global or regional) Performance at least 2 SD below the mean in the domains: • Language/Speech • Fine motor functions or coordination • Spatial-visual perception or spatial-constructive skills • Arithmetic skills • Learning or memory skills • Executive functions • Attention • Social skills and behaviour	**2 to 4**	**A**	[12,15,22–25, 36–74,76–90, 92–94,96–106, 110–120]
Fourth Key Recommendation pFAS If facial and CNS abnormalities are present, the **diagnosis of pFAS should be made when prenatal alcohol exposure is confirmed or probable.**	**3 to 4**	**B**	[77,108,109]

*grades of recommendation: A - strong recommendation: "we recommend"; B - recommendation: "we suggest"; 0 - open recommendation "may be considered"EC - expert consensus.

3.1. The diagnosis of alcohol related birth defects (ARBD)

Alcohol related birth defects (ARBD) should not be used as a diagnosis in Germany (in accordance with CDC, Canadian Guidelines and 4-Digit Diagnostic Code) due to the lack of alcohol related specificity of the malformations and the lack of evidence for ARBD as a clear disease entity (expert consensus) [121].

3.2. General information regarding the interdisciplinary assessment of FASD

Any professional working in the health or social care system for children who identifies abnormalities in one of the diagnostic areas should proceed to assess the other three diagnostic areas or refer the assessment to other professionals with appropriate qualifications (expert consensus).

Professionals, including nurses, midwives, social workers, physiotherapists, speech therapists, occupational therapists, psychologists, psychotherapists, physicians in gynaecology and obstetrics, paediatricians including neonatology, intensive care, paediatric neurology, developmental medicine, child and adolescent psychiatry, general practitioners, and public health services practitioners, should be sensitised to the clinical presentations of fetal alcohol spectrum disorder (FASD). They should be encouraged to report any reasonable suspicion of FASD and to initiate the necessary diagnostic process.

The diagnosis of FASD should involve at least a medical doctor and a psychologist. In infants and toddlers, the assessment should involve a developmental neurologist. A multimodal and interdisciplinary assessment of the child suspected of FASD is strongly recommended (expert consensus) as 1) the disorder is very complex with different medical and neurocognitive dysfunctional profiles, 2) there are significant functional impairments in different areas of life, 3) the impairments can change depending on the developmental age, and 4) the differential diagnosis must be taken into account.

3.3. General information regarding diagnosis in different ages

The diagnostic criteria of FASD are often difficult to apply to newborns as the face may still be swollen or deformed due to the birth. In addition, higher cognitive processes, belonging to the criterion "Functional CNS abnormalities", cannot be detected at this young age.

When assessing functional CNS abnormalities, it should be noted that many psychological tests can only be used once the child reaches a certain age. Standardised developmental tests (e.g., Bayley Scales of Infant Development) should be used instead, when diagnosing very young children. The reduction of performance in certain areas is very difficult or impossible to evaluate in infancy and sometimes also in toddlerhood. For this age group, the assessment of functional CNS abnormalities, and therefore the diagnosis of FASD, depends on an experienced developmental neurological assessor. Clinical experience shows that FAS can sometimes (rather rarely) be diagnosed from birth, but pFAS and ARND cannot. Depending on the test procedure required for the respective age of the child, FASD can often only be diagnosed with certainty at preschool or school age. Nevertheless, if prenatal exposure to alcohol is known, children should be continuously monitored and re-evaluated in terms of developmental diagnostics and parents/caregivers should be proactively supported.

In adolescence and adulthood, we often see the facial features become less pronounced and the growth impairments diminish. It therefore makes sense to use the medical check-up booklet with the growth percentiles in childhood and non-smiling toddlers' or children's photos for assessment. Missing history of prenatal alcohol exposure and

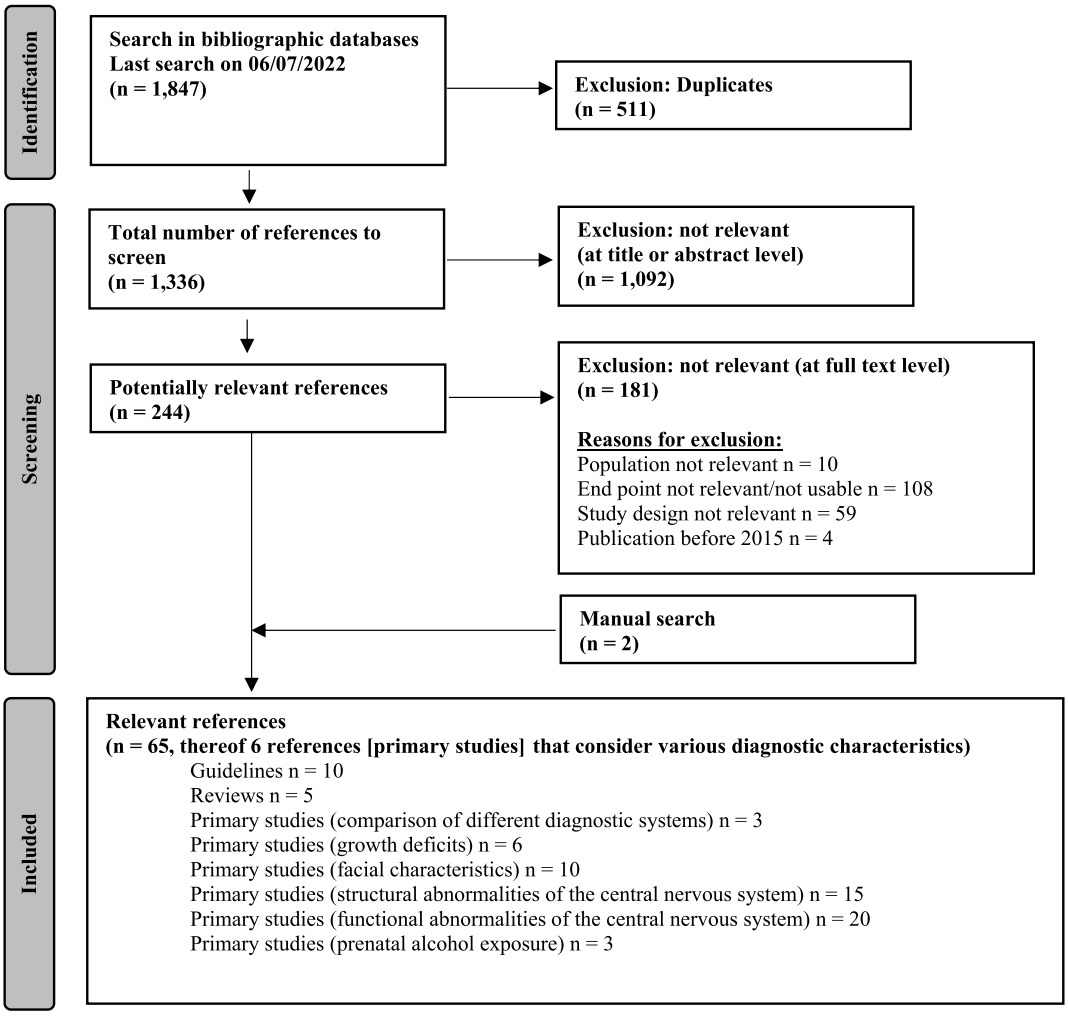

Fig. 1. Flowchart of the systematic literature search.

an increase in comorbidities during adolescence can also complicate the diagnosis.

3.4. Expert consensus and background information regarding the diagnostic pillar "growth deficits"

Body weight and length should always be measured if FAS is suspected. The results of the previous measurements should be taken into account and growth curves created (expert consensus).

It should be ruled out that the growth disorder can be explained solely by other causes such as familial short stature or constitutional developmental delay, prenatal deficiencies, skeletal dysplasia, hormonal disorders, genetic syndromes, chronic diseases, malabsorption, malnutrition or neglect. Other causes of growth failure should be clinically investigated, and, if necessary, ruled out by further diagnostics such as laboratory parameters or imaging procedures (expert consensus).

3.5. Expert consensus and background information regarding the diagnostic pillar "facial characteristics"

To measure the upper lip and philtrum, the Lip-Philtrum Guide (for Caucasian/Asian and African ethnicity) can be used, with five photos corresponding to a five-point Likert scale (see Fig. 2). Measurements with four and five out of five points on the scale are considered pathological (note: it is quite possible that one of these two features is in the conspicuous and one in the inconspicuous range).

The palpebral fissure length can be measured directly on the patient using a transparent flexible ruler or on a photograph of the patient with a reference scale (e.g., 1 cm dot glued to the forehead) (see Fig. 3). A computer program from Hemingway et al. (https://depts.washington.edu/fasdpn/htmls/face-software.htm) can be used to evaluate the length of the palpebral fissure determined using the glued-on reference point. This takes into account the curvature of the eye, which, if neglected, results in the palpebral fissure length being incorrectly assessed as too short. Attempts to glue the reference point directly under or above the eye to mimic the curvature of the eye through the glued point are discussed. Artificial intelligence methods for the measurement of the palpebral fissures are currently developed [122,123]. For the assessment of palpebral fissure length in children with suspected FASD from the age of 6 years, the Clarren et al. palpebral fissure percentile curves should be used [35], for children under the age of 6 years the Strömland et al. percentile curves [124] (expert consensus). Children of African ethnicity cannot be assessed using the two palpebral fissure length percentile curves because, according to Hemingway, the normal value for palpebral fissure length is approximately one standard deviation greater than for children of Caucasian and Asian ethnicity [34].

The guideline group considers the development of up-to-date palpebral fissure length percentile curves, especially for children aged 0–6 years and for different ethnicities, to be urgently needed.

Table 4
Key recommendations for the diagnosis of alcohol related neurodevelopmental disorder (ARND).

Diagnostic recommendations	Level of Evidence	Grade of Recommendation	Related literature
First Key Recommendation ARND For the diagnosis of ARND **all criteria 1 and 2** should be present 1. Abnormalities of the central nervous system (CNS) 2. Prenatal alcohol exposure: confirmed	**EC**		
Second Key Recommendation ARND To fulfil the criterion **"CNS abnormalities**" at least three of the following deficits, that are not adequate for age and that cannot be explained solely by the familial background or social environment should be found (all bullet points equal): • Global intellectual deficit at least two standard deviations below the mean or significant combined developmental delay of children ≤2 years • Epilepsy • Microcephaly ≤10. Percentile or structural CNS malformation (global or regional) •Performance at least 2 SD below the mean in the domains: •Language/Speech •Fine motor functions or coordination •Spatial-visual perception or spatial-constructive skills •Arithmetic skills •Learning or memory skills •Executive functions •Attention •Social skills and behaviour	**2 to 4**	**A**	[12,15,22–26, 36–56,58–74, 76–106, 110–120]
Third Key Recommendation ARND If CNS abnormalities are present, the **diagnosis of ARND should be made when prenatal alcohol exposure is confirmed.**	**3 to 4**	**A**	[77,108,109]

*grades of recommendation: A - strong recommendation: "we recommend"; B - recommendation: "we suggest"; 0 - open recommendation "may be considered"EC - expert consensus.

3.6. Expert consensus and background information regarding the diagnostic pillar "CNS abnormalities"

As measuring the head circumference is a non-invasive procedure and has no side effects for the child, the head circumference should always be measured if FASD is suspected. The results of the previous measurements should be taken into account and head circumference curves created (expert consensus). It should be ruled out that the microcephaly or structural malformation is solely due to other causes such as familial microcephaly, genetic syndromes, metabolic disorders, prenatal deficiency, other toxic damage, infection, maternal diseases or chronic diseases of the child. If the microcephaly is borderline, a neuropsychological testing and other differential diagnosis are recommended.

If facial abnormalities, growth abnormalities and microcephaly are present, diagnostic imaging is not required to diagnose FASD (expert consensus). If necessary and depending on the clinical picture and availability, structural cranial magnetic resonance imaging (c-MRI), functional c-MRI, diffusion tensor imaging (DTI) or other methods can be used to detect structural CNS malformations.

In order to achieve a high sensitivity (correct recognition of FASD) and a high specificity (avoidance of overdiagnosis), an assessment of the cognitive and socio-emotional abilities by an experienced examiner is recommended (expert consensus).

If facial characteristics and growth deficits are present, but microcephaly is absent, a psychological assessment should be used to diagnose FAS. Functional CNS abnormalities should be evaluated using standardised, normative psychological tests and a psychological or medical behavioural assessment of the child for the diagnosis of FASD. The psychological diagnosis should primarily assess the areas typically affected in children with FASD. Due to the inconsistency of the literature, it is not possible to definitively determine which psychological test procedures should be used.

It should be noted that in some areas of CNS functioning, standardised tests are not available or are not sufficiently valid to represent the child's performance in the respective CNS domain in everyday situations. In these cases, a critical clinical examination of CNS function is required, taking into account the relevant everyday functionality recorded in the medical history.

3.7. Expert consensus and background information regarding the diagnostic pillar "Prenatal alcohol exposure"

Alcohol consumption by the biological mother during pregnancy should be evaluated when diagnosing FASD (expert consensus). Recording the mother's alcohol use during pregnancy is particularly difficult. On one hand, many mothers are not asked about their alcohol consumption by the care providers during pregnancy, often for fear of losing trust and breaking off the relationship; on the other hand, the information provided by the mothers is often inaccurate due to social desirability. As many children with FASD live in adoptive and foster families, the anamnesis about the biological parents is often only rudimentary. Measurement options of biomarkers as screening for prenatal alcohol exposure (e.g., ethyl glucuronide, fatty acids ethyl ester, phosphatidyl ethanol) are only partly available in Germany and have the limitation that they cannot provide information on alcohol exposure during the entire pregnancy.

The diagnosis of FASD should be questioned if the biological mother reliably denies prenatal alcohol exposure (PAE). If there is uncertainty about the child's PAE, statements from other caregivers, the child's birth report or other official sources can be used to assess PAE.

4. Discussion

Although there has been a guideline for the diagnosis of FAS in Germany since 2012 and for pFAS and ARND since 2016, the condition is still extremely underdiagnosed. On the one hand, this is due to the fact that dealing with the negative effects of alcohol, which is culturally part of every celebration in Germany and has many other positive connotations, is perceived as uncomfortable and stressful. On the other hand, many doctors and other professionals are unaware of the high prevalence of FASD and the complex effects the disorder has on the life of the child and their family.

Some professionals also shy away from diagnosing because it is very time-consuming and labour-intensive and are sometimes arguing that the condition cannot be cured anyway. However, the diagnosis can generate a concept of the disorder that can give the affected child, their caregivers and the professionals a clearer picture of the cause and

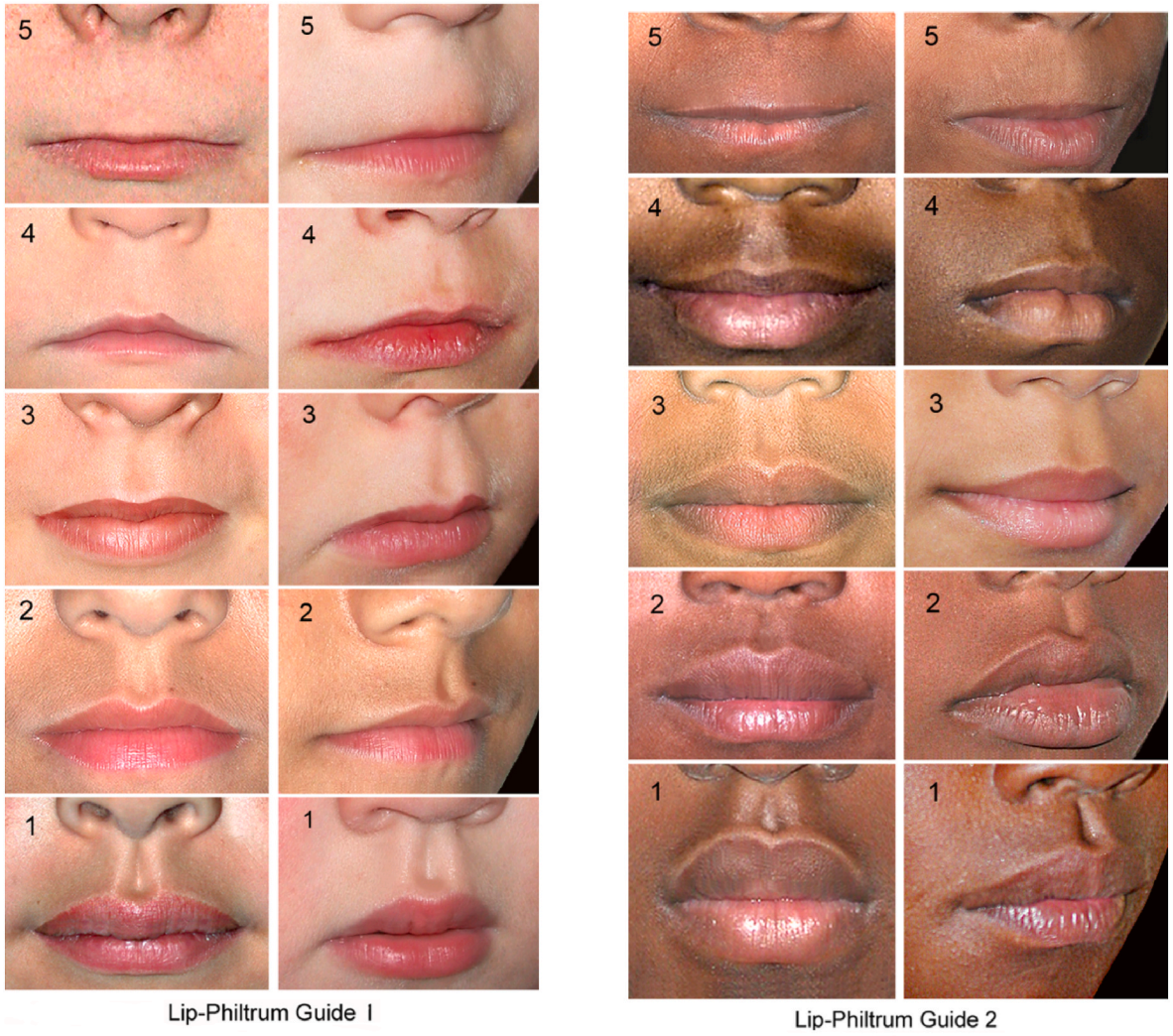

Fig. 2. Lip-Philtrum Guide: left for Caucasian ethnicity, right for African ethnicity (©2024, Susan J Hemingway PhD, University of Washington).

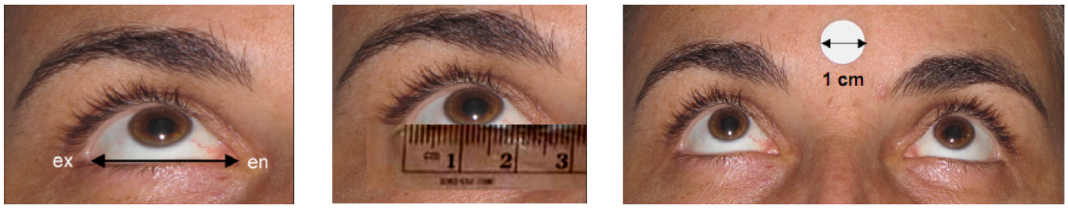

Fig. 3. Measurement of the palpebral fissure length from the endocanthion (en) to the exocanthion (ex) (©2024, Prof. Mirjam N Landgraf, LMU University of Munich).

consequences of the disability, including avoiding causal misattribution, initiating useful therapeutic options, identifying support needs and factors that may improve prognosis. This can significantly improve disease acceptance and relieve the burden on the child's family and wider support system.

A further challenge in the identification of FASD is posed by the fact that certain characteristics of affected individuals may change as they grow older. While facial features and growth deficiencies are common in childhood (especially in FAS), they may become less noticeable in adolescence or adulthood. In early childhood, individuals with FASD may exhibit minimal or no apparent abnormalities in central nervous system (CNS) function. However, as they enter adolescence, many develop issues related to executive functions, behaviour and attention. As a result, diagnosing FASD relies on experienced assessments of development in early childhood and comprehensive neuropsychological evaluations throughout later childhood, adolescence, and adulthood. To assess CNS abnormalities effectively, neuropsychological tests and tools undergo scrutiny for their quality, including standardization, reliability, and validity – not only for the artificial test situation but for everyday life.

During the diagnostic assessment, healthcare providers need to be aware of the wide range of factors contributing to central nervous system abnormalities, in addition to PAE, such as abandonment, nutritional deficiencies, and exposure to other substances of abuse during pregnancy.

Additionally, to accurately diagnose FASD, it is essential to consider

differential diagnoses and rule out other disorders e.g. genetic conditions that may present with similar symptoms. Dysmorphology diagnosis can be particularly challenging due to the variability in ethnic traits and the lack of comprehensive reference standards for diverse populations. Ethnic and genetic differences can affect the phenotypic expression of FASD, making it difficult to apply uniform diagnostic criteria across all ethnicities. While artificial intelligence tools offer a more objective approach to assessing dysmorphologies, they currently struggle to fully accommodate ethnic diversity and the complexity of phenotypic variations [125,126].

Based on studies on prognosis [5,6], we know that early diagnosis of FASD in childhood is a factor for a better prognosis. Therefore, a ubiquitous, standardised, correct and early diagnosis is extremely important for these children.

The guideline presented here is outstanding regarding its methodological approach. It has been developed in accordance with international methodological standards, and additionally, with the involvement of an external institute for literature search and standardised evidence evaluation, as well as with a structured consensus finding by means of a nominal group process of a representative guideline group with an external moderator. In this respect, it differs qualitatively from other international FASD guidelines [127,128]. Unlike most other guidelines, which are primarily developed outside of Europe, our guideline has been specifically designed with a European context in mind. This makes it more applicable and adaptable for use across European healthcare systems, ensuring that it better addresses the unique challenges and needs present within this region. Therefore, the diagnostic recommendations contained in the guideline presented here are easy to apply in everyday clinical practice and support less experienced colleagues in the clarification of FASD.

Nevertheless, it must be noted that the evidence for the diagnostic criteria for FASD is still rather low.

One of the reasons is that there is no gold standard for the diagnosis, which makes it difficult to compare and summarize results, when different diagnostic systems were used. There are various obstacles for a gold standard:

Almost all studies are based on maternal/parental information on alcohol consumption, a method prone to recall and social desirability bias and other limitations which can compromise the accuracy of the data. This underscores the importance of incorporating reliable biomarkers as objective measures to more accurately identify PAE.

However, there are no biomarkers of prenatal alcohol exposure that are valid for the whole pregnancy and provide high levels of sensitivity and specificity.

Furthermore, the available biomarkers can only detect alcohol exposure and cannot diagnose FASD or predict the severity of its effects.

In this context it is important to notice that the precise effects of alcohol consumption during pregnancy remain not fully understood due to the complexity of factors involved, such as timing, dosage, and individual biological differences. This makes it challenging to draw definitive conclusions, and further investigations are required to comprehensively assess the full range of effects alcohol may have on fetal development.

Another reason for the uncertainty of evidence is that the diagnostic criteria for FASD in international studies are often validated on children who have previously already been diagnosed with FASD. This results in an incorporation bias.

There is much international debate about standardising the diagnosis of FASD, but no agreement has been reached yet, and the diagnostic criteria for FASD vary widely from guideline to guideline [127–129]. This means that the same child might receive a different diagnosis, when being assessed in different countries. Therefore, we believe that unifying the diagnostic criteria for FASD would not only enhance research consistency but also improve health outcomes for individuals affected by this condition.

For the German guideline, we tried to use the most objective methodological strategies possible, commissioned an external, independent institute to assess the evidence, and consulted a methodological advisor from the Association of the Scientific Medical Societies in Germany (AWMF) for all consensus processes. This process is unique in Europe, so the German guideline reflects the best available medical knowledge for the diagnosis of FASD in children and adolescents and can be used throughout Europe.

Nevertheless, this means that due to a lacking gold standard the diagnosis should be made with caution and clinical expertise and low-threshold differential diagnostic considerations should be made. Additionally, it is important to recognise that there may be stigma associated with the diagnosis and that this may not only affect the individual diagnosed with FASD, but may have wider implications for the whole family. The family, and particularly the child and the biological mother, may face social stigma and judgment, which can exacerbate the challenges they already face. This stigma can impact their emotional well-being, social interactions, and access to support and resources. Therefore, not only cautious clinical diagnosis but also further research into biomarkers, particularly in genetics and epigenetics, is essential. Such advancements are expected to improve diagnostic accuracy in the future and help reduce the incidence of under- or misdiagnosed cases.

Comprehensive training and ongoing education programs for health care providers are critical for reducing underdiagnosis, ensuring accurate diagnosis, understanding the complexity of FASD, and applying the guidelines appropriately.

In order to increase the knowledge of FASD, the German guidelines does not only recommend diagnostic criteria for identifying FASD but also address maternal risk factors for alcohol consumption during pregnancy and additional risk factors associated with the development of FASD.

Therefore, the development of the guideline is intended not only to support clinical practice, but also to increase the awareness and knowledge of health professionals about risk factors for FASD and the specific characteristics of children and adolescents with this disease. Successfully informing the public about the lasting adverse effects of prenatal alcohol exposure requires the involvement of well-trained and experienced professionals within the healthcare and social services sectors who are sufficiently aware of the issue. Therefore, the guideline may also have a positive effect by improving the education of prospective parents about the risk of prenatal alcohol exposure for their child, raising the percentage of alcohol-free pregnancies and reducing the incidence of FASD.

Additionally, Germany - and many other countries in Europe - also needs to create financial opportunities and area-wide structures to diagnose and treat children with FASD and to support their families so that they can cope with the challenges of everyday life with their children.

Further research is urgently needed, not only into the certainty and reliability of the diagnosis, but also into effective support measures and protective factors for the long-term outcomes in the areas of everyday functioning and quality of life for children with FASD.

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Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2024.11.002.

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