Accepted Manuscript

Submission Date: 2024-12-17
Accepted Date: 2025-02-18
Accepted Manuscript online: 2025-02-27

Neuropediatrics

First evidence-based guideline for interventions in FASD

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DOI: 10.1055/a-2547-4610

Please cite this article as: Strieker S, Heinen F, Ziegler A et al. First evidence-based guideline for interventions in FASD. Neuropediatrics 2025. doi: 10.1055/a-2547-4610

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Gemeinsame Bundesausschuss (http://dx.doi.org/10.13039/501100014840), 01VSF21012

Abstract:
BACKGROUND
Prenatal alcohol exposure causes disruptions in brain development. The resulting disorder, fetal alcohol spectrum disorder (FASD), cannot be cured, but interventions can help improve the daily functioning of affected children and adolescents and the quality of life for the entire family.
OBJECTIVE
The aim of the German guideline version 2024 is to provide validated and evidence-based recommendations on interventions for children and adolescents with FASD.
METHODS
We searched for international guidelines and performed a systematic literature review and a hand search to identify literature (published 2012–2022) on interventions for children (0–18 years) with FASD. The quality of the literature was assessed for predefined outcomes using the GRADE method (Grading of Recommendations, Assessment, Development and Evaluation). We established a multidisciplinary guideline group, consisting of 15 professional societies, a patient support group and 10 additional experts in the field. The group agreed on recommendations for interventions based on the systematic review of the literature and formulated additional recommendations, based on clinical experience/expert evidence in a formal consensus process.
RESULTS
No international guideline focusing on interventions for patients with FASD was found. 32 publications (4 systematic reviews, 28 original articles) were evaluated. The analysis resulted in 21 evidence-based recommendations and 26 expert consensus, covering the following topics: neuropsychological functioning, adverse effects of therapy, complications/secondary conditions, quality of life, caregiver burden, knowledge of FASD, and coping and self-efficacy.
CONCLUSION
The German guideline is the first internationally to provide evidence-based recommendations for interventions in children and adolescents with FASD.

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ePub Table 1: Members of the guideline group

Guideline coordinators - Institutions	Names
Ludwig-Maximilians-University of Munich (LMU), Department of Neuropediatric, Social Pediatric Centre	Prof. Mirjam Landgraf MD
Ludwig-Maximilians-University of Munich (LMU), Department of Neuropediatric, Social Pediatric Centre	Sonja Strieker
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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 (Vive Director)
German Scientific Societies and Professional Associations	Representatives
Society of Neuropediatric (Germany, Austria, Switzerland) (GNP)	Prof. Mirjam Landgraf MD
German Society of Pediatrics and Adolescent Medicine (DGKJ)	Prof. Florian Heinen MD

German Society of Social Pediatrics and Adolescent Medicine (DGSPJ)	Juliane Spiegler MD
German Society of Gynecology and Obstetrics (DGGG) German Society for Prenatal and Obstetric Medicine (DGPGM)	Dietmar Schlembach MD
German Society of Neonatology and Pediatric 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
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German Association of Midwives (DHV)	Andrea Köbke
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Federal Association of Physicians of the Public Health Services (BVÖGD)	Gabriele Trost-Brinkhues MD
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	Substitution: Johanna Thünker
FASD Experts	Names
Former professor of FASD Centre at Charité University, Berlin	Prof. Hans-Ludwig Spohr
Social Pediatric Centre of Charité University, Berlin	Heike Wolter
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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, specialized in FASD	Gila Schindler
German Patient Support Group FASD Deutschland e.V.	Representatives
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	Substitution: Katrin Lepke
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ePub Document 1: Publications included in the systematic evidence classification.

Original Publications

1. Boroda, E., Krueger, A. M., Bansal, P., Schumacher, M. J., Roy, A. V., Boys, C. J., Lim, K. O., & Wozniak, J. R. (2020). A randomized controlled trial of transcranial direct-current stimulation and cognitive training in children with fetal alcohol spectrum disorder. Brain Stimul, 13(4), 1059-1068. https://doi.org/10.1016/j.brs.2020.04.015
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Systematic Reviews

1. Flannigan, K., Coons-Harding, K. D., Anderson, T., Wolfson, L., Campbell, A., Mela, M., & Pei, J. (2020). A Systematic Review of Interventions to Improve Mental Health and Substance Use Outcomes for Individuals with Prenatal Alcohol Exposure and Fetal Alcohol Spectrum Disorder. Alcohol Clin Exp Res, 44(12), 2401-2430. https://doi.org/10.1111/acer.14490
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4. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903

ePub Document 2: Risk of bias assessment.

Risk of bias assessment – original studies

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
´Smiarowska et al. (2022) (1) Uncontrolled intervention study	- Inclusion criteria: children (> 6 years old) with ADHD and hPAE who did not benefit from cognitive behavioural therapy for last 6 months or who have severe ADHD symptoms and dysfunctional environmental functioning - Exclusion criteria: psychiatric or developmental disorders - Enrolled: n = 303 - Included: n = 114 - Age: > 6 years	NA	MPH: - 20 mg MPH hydrochloride or 36 mg MPH - Maximum dose (60 mg MPH hydrochloride or 36 mg MPH) was used only in individual cases - Daily doses for 4 weeks	NA	- Tolerability (depending on polymorphisms) - Severity of ADHD symptoms (depending on polymorphisms)	Tolerability: 104 successfully treated: 3 without improvement, 7 discontinued due to adverse effects (occurred at the time of drug introduction and decreased after introduction of a modified form of MPH); no cardiotoxic effects or life-threatening symptoms; Borderline significance between adverse effects and the COMT rs4680 minor allele (G > A) ($p < 0.049$) Severity of ADHD: - All children: treatment was effective in > 90 % of children - Children with morphological features of FASD: significant reduction in symptoms of hyperactivity and impulsivity ($p < 0.0001$); no improvement in attention deficits ($p = 0.2024$)	- No specific age range - Missing source of recruitment and recruitment process - Very short treatment period - No international diagnostic valid instrument for severity questionnaire - Genomic DNA was extracted and genotyping for COMT rs4680, DRD2 rs1076560, and rs1800497 SNPs was used - No monitoring of adherence - Children with morphological	Low for effectiveness Moderate for adverse effects (ROBINS-I modified

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							- Children without morphological features of FASD: significant improvement in attention ($p < 0.001$); reduction in hyperactivity ($p = 0.0163$); no significant reduction in impulsivity ($p = 0.1274$) No association of the studied polymorphisms: DRD2 rs1076560: C > A or DRD2 rs1800497: G > A with the efficacy or safety of MPH	features of FASD had significantly higher doses of MPH - No subanalyses of sex, medicine	
Nguyen et al. (2016) (2) **RCT (multisite, randomized, double-blinded, placebo-controlled, parallel-group clinical trial)**	- Inclusion criteria: children with confirmed hPAE; primary English speakers - Exclusion criteria: head injury, substantial physical or psychiatric disability; any other causes of mental deficiency; prescription of medication with risk of atherosclerosis - 5–10 years old Choline group: - Assigned: n = 30 - Received: n = 29 - Lost to follow-up: n = 1 - Completed: n = 28 - Analysed with intention-to-treat: n = 29 Placebo group: - Assigned: n = 28 - Received: n = 26 - Lost to follow-up: n = 2 - Completed: n = 24 - Analysed with intention-to-treat: n = 26		Discontinued intervention: n = 0	Choline: - 625 mg choline (in form of a glycerophosphocholine liquid concentrate (5.25 ml/d)) - Daily doses for 6 weeks	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 6 weeks	- Neuropsychological measures of memory, executive function, attention and hyperactivity - Association between treatment compliance/dietary choline intake and outcomes - Tolerability	Cognitive performance: - Choline group did not differentially improve in any cognitive performance domain (no group or group x time interaction) - Treatment compliance and mean dietary choline intake were not predictive of cognitive performance - No significant interaction of group x time x age group in any cognitive outcome variable Compliance: high treatment	- Very small sample size in subgroup analyses of age - Intention-to-treat analyses (subanalyses of children completing the study did not change results) - Children without FASD diagnosis included	Low (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								compliance in both groups (about 96 %) Tolerability and adverse events: - Significantly more children in choline group reported at least 1 adverse event - No serious adverse events		
Wozniak et al. (2013) (3) **RCT (double-blind, randomized, placebo-controlled trial) pilot study**	- Inclusion: Children with FASD diagnosis - Exclusion: developmental or neurological disorder; other medical conditions affecting the brain. - No exclusion: psychiatric co-morbidities (ADHD) - 2,5–4,9 years old Choline group: - Assigned: n = 13 - Received: n = 10 - Lost to follow-up: n = 0 - Completed: n = 9 - Analysed with intention-to-treat: n = 10	Placebo group: - Assigned: n = 12 - Received: n = 10 - Lost to follow-up: n = 1 - Completed: n = 8 - Analysed with intention-to-treat: n = 10	Choline: Discontinued: n = 1 (refused to test agent for more than 1 month)	Placebo: Discontinued: n = 1 (declined to continue)	Choline: - 1.25 g choline bitartrate powder delivering 500 mg choline - Daily doses for 9 months	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 9 months	- Feasibility of parental administration - Tolerability - Serum choline levels	Feasibility: - Compliance: 82 % - 87 % - No evidence for dietary confounding Tolerability: - Minimal adverse effects: no group differences on all adverse events except for a fishy body odor in the choline group (p = 0.011) - In both groups: taste problems at least once (55 %); non-standard administration at least once (75 %) Serum choline level: - Choline group increased choline at all time points: 1 month (p = 0.004), 6 months (p < 0.001), and 9 months (p < 0.001) - Choline group increased betaine	- No child living with biological parents - Prenatal drug use was suspected with alcohol being the dominant substance (n = 14) - Reasons for drop-out: not related to study; lost to follow-up; refused dose after one time trying it - Potential unblinding due to fishy body odor - Not all children at each testing	Low (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								concentration at all time points: 1 month (p = 0.04), 6 months (P = 0.03), and 9 months (p = 0.04) - No changes in phosphatidylcholine - Choline group had higher sphingomyelin concentrations at baseline (p = 0.04) and months 1 (p = 0.05), but no differences in months 6 (p = 0.25) and 9 (p = 0.91)	point	
Wozniak et al. (2015) (4) **RCT (randomized, double-blind, placebo-controlled pilot trial)**	- Inclusion: Children with confirmed hPAE or suspected hPAE with dysmorphic faces and cognitive deficits - Exclusion: developmental or neurological disorder; traumatic brain injury; other medical conditions. - No exclusion: psychiatric co-morbidity (ADHD or learning disorder) - 2,5–5 years old		Choline: Discontinued: n = 5 (declined to continue: n = 4; refused intervention: n = 1)	Placebo: Discontinued: n = 3 (declined to continue)	Choline: - 1.25 g choline bitartrate powder delivering 500 mg choline - Daily doses for 9 months	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 9 months	- Neurocognitive functioning (particularly hippocampal-dependent memory) - Feasibility - Serum choline levels - Tolerability	Global cognitive functioning: no main effects of treatment and no interaction effect The Mullen Early Learning Composite was correlated (with age controlled for) with EI delayed performance for items (partial r = 0.56, P < 0.001) and ordered pairs (partial r = 0.47, P < 0.001) at baseline but not at the 9-month visit (p > 0.17 for all). Hippocampus-dependent long-term memory: - No significant main effects of treatment on EI delayed	- All children received the same dosage regardless their weight - Intention-to-treat analysis - Due to different group distributions age, race, and FASD diagnosis were included as covariates - Immediate recall performance showed no improvement in	Low (RoB-2)
	Choline: - Assigned: n = 34 - Received: n = 31 - Lost to follow-up: n = 0 - Completed: N = 26 - Analysed with intention-to-treat: n = 31	Placebo: - Assigned: n = 31 - Received: n = 29 - Lost to follow-up: N = 1 - Completed: n = 25 - Analysed with intention-to-treat: n = 29								

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								memory performance - race and FASD diagnosis as no moderators - Age as a moderator: o subanalysis: splitting participants into a younger group consisting of 2.5 to ≤ 4.0-year-olds (n = 30; placebo: n = 13; choline: n = 17) and an older group consisting of > 4.0–5.0-year-olds (n = 30; placebo: n = 16; choline: n = 14) o Largest improvement in delayed EI performance in the young choline group. - For items: t test [t(28) = -2.41, p = 0.023]; d = 0.54 => young choline group showed an increase of 21 % compared with	choline group for items; but for ordered pairs the choline group performed worse than placebo - Improvements in delayed memory in the young group was only present after controlling for immediate recall performance - Potential ceiling effect in EI: young choline group had slightly lower delayed EI performance than the other groups at baseline	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								- 7 % in the young placebo group - For ordered pairs: [t(28) = -2.18, p = 0.038]; d = 0.50 => young choline group showed an increase of 28 % compared with 16 % in the young placebo group o No significant differences for the older age groups Feasibility: - Compliance: dose on 88 % of days - Diet: no group differences regarding compliance or dietary changes Serum choline levels: Significant increase in serum choline (102 %; p < 0.0001) and betaine (106 %; p < 0.0001) in choline group Tolerability: fishy body odor as the only adverse event		
Wozniak et al. (2020	- Inclusion: Children with confirmed hPAE or suspected hPAE with dysmorphic faces and cognitive deficits; supplement adherence in		Choline: Initial trial: Discontinue	Placebo: Initial trial:	Choline: - 1.25 g choline bitartrate powder	Placebo: - Equivalent doses of an oral	Potential long-term cognitive and	General cognitive functioning: - Choline	- No measures of serum cholin	Low (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
) (5) 4-year follow-up of a RCT (randomized, double-blind, placebo-controlled trial)	initial trial > 50 % of days - Exclusion: developmental or neurological disorder; traumatic brain injury; other medical conditions. - No exclusion: psychiatric co-morbidity (ADHD or learning disorder) - 2,5–5 years old in initial trial		d: n = 5 (declined to continue: n = 4; refused intervention: n = 1)	Discontinued: n = 3 (declined to continue)	delivering 513 mg choline - Daily doses for 9 months	inactive placebo treatment - Daily doses for 9 months	behavioural implications (intelligence, memory, executive functioning, and behaviour)	group had higher non-verbal IQ (8 % difference; (F1, 28) = 5.17; p = 0.03; ηp2 = 0.17); and higher working memory scores (11.7 % difference; F(1, 28) = 7.74; p = 0.01; ηp2 = 0.23) - Components of non-verbal IQ: significant group effects in 2 of 5 components: non-verbal Visual-Spatial Reasoning with Choline group showing better performance (28.9 % difference; F(1, 29) = 9.93; p = 0.004), and non-verbal Working Memory with Choline group showing better performance (26.8 % difference; F(1, 29) = 6.37; p = 0.018) - No significant differences in Verbal IQ; Fluid Reasoning; Knowledge; Quantitative Reasoning; Visual-Spatial Processing and Full-Scale IQ	e level - Dietary intake as a potential mediator	
	Choline: Initial trial: - Assigned: n = 34 - Received: n = 31 - Lost to follow-up: n = 0 - Completed: n = 26 - Analysed with intention-to-treat: n = 31 Follow-up: - Lost to follow-up: n = 9 - Analysed: n = 15	Placebo: Initial trial: - Assigned: n = 31 - Received: n = 29 - Lost to follow-up: n = 1 - Completed: n = 25 - Analysed with intention-to-treat: n = 29 Follow-up: - Lost to follow-up: n = 8 - Analysed: n = 16								

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								Memory functioning: No significant group differences regarding the EI paradigm; age was not a significant modulator; In NEPSY-II choline group scored significantly higher in Memory for Names Delayed (37.9 % difference; p = 0.04; d = 0.77) Executive functioning: No group differences in the Dimensional Change Card Sort Test; but a trend toward higher performance in the Flanker Inhibitory Control Test in the choline group compared to placebo (13.5 % difference; p = 0.08; d =0.66) Behavioural and emotional functioning: Choline group had significantly lower scores in the parent-reported scale for ADHD problems (estimated marginal mean = 62.1; SE = 2.1) compared to placebo group (estimated marginal mean = 69.0; SD = 2.0) (10.5% difference; F(1,28)=5.57; p=0.026; ηp2 =0.17)		
Smith et	- Inclusion: Children with confirmed hPAE or suspected hPAE with dysmorphic faces		Choline: Initial trial:	Placebo: Initial	Choline: - 1.25 g choline	Placebo: - Equivalen	Correlation between	14 SNPs within the	Small number	Low (RoB-

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
al. (2021) (6) **Retrospective analysis of a RCT (randomized, double-blind, placebo-controlled trial)**	and cognitive deficits; supplement adherence in initial trial > 50 % of days; providing blood sample for genomics - Exclusion: developmental or neurological disorder; traumatic brain injury; other medical conditions. - No exclusion: psychiatric co-morbidity (ADHD or learning disorder) - 2,5–5 years old in initial trial		Discontinued: n = 5	trial: Discontinued: n = 3	bitartrate powder delivering 500 mg choline - Daily doses for 9 months	t doses of an oral inactive placebo treatment - Daily doses for 9 months	choline-related SNPs and memory and cognition (at study terminus, and 4 year follow-up)	choline transporter gene SLC44A1 were significantly associated with the change-score (pre-/post) on an EI sequential memory task (p = 0.04969) Same 14 SNPs + 2 SNPs within SLC44A1 were associated with change scores for adjacent pairs of items from the sequence (p = 0.023) Only participants in the choline group who had these variants were more likely to show improvement in the memory task (pre-/post). Some SNPs were associated with improved performance in the working memory measure of the Stanford-Binet Intelligence Scale, version 5, at 4 year follow-up, in the EI immediate memory task at baseline, in the NIH Toolbox Dimensional Card Sort Test at 4 year follow-up, and in change-score measures from baseline to 9 months for the Immediate Memory Task in the EI	of participants with specific SNPs	2)
	Choline: Initial trial: - Assigned: n = 34 - Received: n = 31 - Lost to follow-up: n = 0 - Completed: n = 26 - Blood sample: n = 26 - Analysed with intention-to-treat: n = 31 Follow-up: - Lost to follow-up: n = 11 - Analysed: n = 15	Placebo: Initial trial: - Assigned: n = 31 - Received: n = 29 - Lost to follow-up: n = 1 - Blood sample: n = 26 - Completed: n = 25 - Analysed with intention-to-treat: n = 29 Follow-up: - Lost to follow-up: n = 9 - Analysed: n = 16								

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
Boroda et al. (2020) (7) **RCT**	- Inclusion criteria: documented history of heavy PAE; or suspected of heavy PAE with full-FAS diagnosis based on dysmorphology; at baseline characterized according to modified IOM criteria - Age: 9–16 years tDCS: - Assigned: n = 20 - Lost to follow-up: n = 0 - Analysed: n = 19	Sham stimulation augmented (sham): - Assigned: n = 24 - Lost to follow-up: n = 2 - Analysed: n = 19	tDCS: Discontinued: n = 1 (stimulation discomfort)	Sham: Discontinued: n = 3 (stimulation discomfort: n = 1, time commitment: n = 2)	tDCS group: 2 parallel components: - Cognitive training: 5 tasks from BrainHQ focussing on working memory and attention. Tasks were completed 4 times (total of 46 minutes) during each of 5 weekly sessions. - tDCS: transcranial stimulation was initiated 30s (at 2mA intensity) prior cognitive training and lasted 13 min. Afterwards, it turned off and stayed off for 20 min. Then it turned on again for 13 min.	Sham: 2 parallel components: - Cognitive training: 5 tasks from BrainHQ focussing on working memory and attention. Tasks were completed 4 times (total of 46 minutes) during each of 5 weekly sessions. - Sham: transcranial stimulation ramped up to 2mA over the course of 30s, ramped down to 0mA over 30s and remained at 0mA.	- Feasibility - Tolerability - Cognitive gains (near/far transfer)	Tolerability: No significant differences for tDCS related side-effects between the groups and no serious adverse events Near transfer of cognitive gains: - For visuospatial working memory, a significant effect of time was observed ($F(1, 144) = 2.46$, $p = 0.047$), with both groups showing improvement over the visits, but no significant effect for tDCS versus sham ($F(1, 39) = 0.017$, $p = 0.911$) or an interaction effect ($F(1, 144) = 4.41$, $p = 0.612$). No meaningful between group effect size. - In the continuous performance test tDCS performed significantly better over time than sham ($F(1, 39) = 4.31$, $p = 0.043$). No significant overall effect of time ($F(1, 144 = 1.36$, $p = 0.247$) or an interaction ($F(1, 144) =$	- Main effect of treatment was only marginally significant and would likely not remain significant after correction for multiple-comparisons. - In cognitive training attention was emphasised and working memory was only trained in 2 tasks - Effects of more training sessions unclear	Low (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								1.46, p = 0.221). Posthoc contrast analyses: significant tDCS versus sham differences at visit 3 (p = 0.033), visit 4 (p = 0.043), and visit 5 (p = 0.046). Medium between group effect size (d = 0.64). Far transfer of cognitive gains: - For the verbal fluency test, no significant effects of tDCS were seen for either letter VF (F(1, 36) = 0.067, p = 0.797), nor category verbal fluency (F(1, 36) = 0.049, p = 0.826). - No treatment effect was seen for the trail making test performance for number sequencing (F(1, 36) = 0.064, p = 0.801), letter sequencing (F(1, 36) = 2.75, p = 0.107), nor combined letter and number sequencing (F1(1, 36) = 0.197, p = 0.659).		
Vidal et al. (2020) (8)	- Inclusion: FASD diagnosis (FAS, pFAS, ARND); 6-18 years of age; with stabilized doses of medication for at least 2 months before the study - No exclusion: comorbidities,		DAT: Discontinued medication: n = 2	TAU: Dropped-out: n = 1; Discontinued	DAT: - 12 manualized sessions in 2 phases (6 individual	TAU: Pharmacological treatment as usual	- Social skills - Internalized symptoma	Social Skills: - A main effect on time [F(1.30) =	- Low power - All participants had	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
RCT (randomized, rater-blinded, controlled pilot trial)	borderline IQ/intellectual disability			medication: n = 2	sessions, 6 group activity sessions - Sessions included 2 certified therapy dogs - Groups of 3-4 patients - Weekly 45-miniute sessions for about 3 months - Pharmacological treatment as usual		tology - Externalized symptomatology - Severity of FASD symptoms.	15.54, p = 0.001] and an interaction time x group with the DAT group being the one who improved more [F(1.30) = 13.82, p = 0.02, d = 0.8]. - Problem behaviour: no interaction of time x group Internalizing symptoms: Main effect of time [F(1.30) = 10.45, p = 0.001], but there was no significant interaction of time x group Externalizing symptoms: Main effect of time [F(1.30) = 12.35, p = 0.001] and also a significant interaction on time x group [F(1.30) = 11.59, p = 0.03, d = 0.56 Severity of FASD Symptoms: Main effect of time [F(1.30) = 12.549, p = 0.001] and also a main effect on time x group interaction with FASD severity decreasing significantly more in the DAT group [F(1.30) = 16.54, p = 0.001, d = 0.5].	ADHD - Effects of DAT only with pharmacological treatment - Maintenance of the results is unclear - No definition of TAU - No clear description of DAT - Results might be due to the intensive treatment sessions and not due to the dogs involved - Big range of age (6-18 years)	
	DAT: - Assigned: n = 19 - Completed: n = 17 - Lost at post-treatment: n = 0 - Analysed: n = 17	TAU: - Assigned: n = 20 - Completed: n = 16 - Lost at post-treatment: n = 1 - Analysed: n = 16								
Kerns et al. (2017) (9)	- Inclusion: Children with diagnosed FASD or Autism Spectrum Disorder who receive Educational Assistant Support within their school		Discontinued: n = 6 (Education Assistant scheduling difficulties)		Caribbean Quest: - Video game with one-to-one support	NA	- Everyday problem behaviour and attention	- Everyday problem behaviour and attention	- Potential bias due to additio	Moderate (ROBINS-I modi

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
Uncontrolled intervention study	program - Exclusion: history of traumatic brain injury, chronic health problem, inability to verbally communicate or diagnosis of an intellectual disability based on information provided by special education staff and parent or caregiver - Age: 6–13 years old - Enrolled: n = 23 - Completed: n = 17 - Analysed: n = 17 (Children with FASD: n = 10 Children with Autism Spectrum Disorder: n = 7)		by a trained and tested educational assistant using metacognitive strategies - Game consisting of 5 hierarchically structured self-adjusting mini-games to improve attention and working memory - 30-minute sessions, 2–3 times a week over a 10-12 week span		skills - Emotional and behavioural strengths - Utility and feasibility - Attention - Working Memory - Academic skills - Children's respond to training	skills: BRIEF and CRS-3 could not be analysed due to very low questionnaire return rates - Emotional and behavioural strength: BERS-2 could not be analysed due to very low questionnaire return rates - Utility and feasibility: 80% reported easy incorporation in school schedule - Attention: sign. reductions in total errors on the KiTAP for distractibility (p = 0.002, d = 0.87) and divided (p = 0.001, d = 0.91) tasks, and no significant reduction of total errors in the flexibility task (p = 0.226, d = 0.31); no differences on the total correct responses of any KiTAP task - Working Memory: significant improvement on the Listening Recall (p = 0.003, d = 0.45) and Counting Recall (p = 0.001, d = 0.61) verbal working memory	nal support services - Possible practice effect - No sub-analysis of disorder type - No manualized version of the Caribbean Quest intervention protocol that includes evidence-based guidelines to assist in metacognitive training - Impact of components of intervention unclear (serious game vs metacognitive training)	fied)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
						tasks from WMTB-C; no significant changes on the WISC-IV verbal and spatial span tasks - Academic skills (AIMSweb): significant reductions in errors on the oral reading fluency task ($p = 0.002$, $d = 1.30$); total number of correct words did not change (children read less quickly, but the read words were more likely to be correct) - Academic skills (interview with Educational Assistants): spelling, reading, and math were ameliorated (no quantitative testing) - Children's respond to training (interview with Educational Assistants): functional improvements in the classroom (improved focus and alertness, decreased hyperactivity, less resistance to engaging in new/challenging activities, increased academic		

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
								engagement and mastery); emotional and social improvements			
Kable et al. (2015) (10) **RCT**	- Inclusion: clinical diagnosis of FAS/pFAS or significant levels of alcohol-related dysmorphia - Exclusion: IQ < 50; diagnosis of mental health problems interfering with learning; no stable placement - Parents needed to complete two workshops (education about neurodevelopmental characteristics of FASD; strategies to deal with behavioural regulation problems) - Age: 3–10 years old - Recruited: n = 68	Centre MILE: Discontinued: n = 1 (session 3-travel and time)	Community MILE: Discontinued: n = 1 (session 4-scheduling conflicts/ travel)	Parents Instruction: Discontinued: n = 0	MILE: - Parents completed workshops and received a manual discussing math learning in children with FASD and strategies for facilitating math learning at home - MILE: Program targeting learning behaviour and math development and focussing on core deficit of mathematical competence (metacognitive control strategies adapted from FAR) - One-on-one individualized tutorial sessions by trained instructor - Weekly home assignments - Weekly sessions for 15 weeks	Parents Instruction: Parents completed workshops and received a manual discussing math learning in children with FASD and strategies for facilitating math learning at home	- Instructor satisfaction - Instructor knowledge - Instructor fidelity - Child's academic outcomes - Parent satisfaction	Instructor satisfaction, knowledge, and fidelity: - High satisfaction and willingness to recommendation - Significant group effect on the knowledge scores ($F(2, 48) = 8.21$, $p < 0.001$, $\eta p2 = 0.255$) with centre-based employees who were not trained in the MILE program receiving lower	- Original treatment plan of 6 weeks was extended to 15 weeks - Detailed instruction training with feedback on the sessions and mock sessions - Children were evaluated by a psychologist or psychology trainee blind to group status - Possible impact of maturation effects as groups differed in days of completion - KeyMath only administered to children ≥ 5 years (N's:	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								scores (X = 8.00, STD = 1.92) than both instructors trained at the centre (X = 9.83, STD = 0.76) or in the community (X = 9.39, STD = 0.41), but no difference between centre-instructors and community-instructors - The session number was positively related to the fidelity score (r = 0.36, p 0.005),	Centre = 9; Community = 14; Parent Instruction = 12) - No results for the instrument adapted from math concepts administered as part of the Bayley Scales of Infant Development 2nd Edition (for children < 5 years) - Raw and standardized scores were analysed - Broad age span (possible floor effects with younger children)	

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
									suggesting that instructors were improving over the course of sessions. A significant effect was found for block ($F(2, 52) = 4.26$, $p < 0.019$) but was not found for site. Higher ratings of fidelity were obtained in the final block of five sessions relative to the initial block of sessions. Child's academic outcomes:		

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								- No significant group*time effect on the individual tests - Using the math summary score from summing the raw scores from Bracken, TEMA, and Handwriting measure: significant time*group effect with MILE groups demonstrating more positive gains in math skills than Parent Instruction group		

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
									(F(2, 41) = 3.4, p < 0.04, ηp2 = 0.139) - Within in the MILE groups, fidelity ratings were significantly positively correlated with change on the total score of Key Math (standard score D: r = 0.48, p < 0.02) and the TEMA (raw score D: r = 0.35, p < 0.04; standard score D: r = 0.45, p < 0.04), but no significant corr		

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
									elations with the raw scores of Key Math, the number of writing score or the total scores from Bracken. Parent satisfaction: - Compared to MILES groups, the Parent Instruction group reported less agreement that child improved in math skills ($p < 0.001$) and that their ability to help child to study had impr		

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								oved ($p < 0.01$) - Centre-MILES group reported more favourable rating than Parent Instruction group on: informative ($p < 0.05$), helpful ($p < 0.05$), improved understanding of FAS/pFAS ($p < 0.01$), and helped child's study habits ($p < 0.05$); - Community-MILE group and Parent Instruction grou		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
										p did not differ significantly		
Kully-Martens et al. (2018) (11) **CCT (not randomized)**	- Inclusion: confirmed PAE or FASD diagnosis - No exclusion: common mental health comorbidities - Enrolled: n = 29 - Age: 4–10 years		MILE: Discontinued: n = 0	SSIS: Discontinued: n = 0		MILE: - No parent workshops - MILE: Program targeting learning behaviour and math development and focussing on core deficit of mathematical competence (metacognitive control strategies adapted from FAR) - One-on-one individualized tutorial sessions by trained instructor - Weekly home assignments - 10–30-minute sessions once/twice a week for 6-8 weeks	SSIS: - The Social Skills Improvement System Intervention: Program focussing on social skills - One-on-one individualized tutorial sessions Weekly home assignments - 10–30-minute sessions once/twice a week for 6–8 weeks	- Mathematical skills - Executive functioning - Working memory - Visuospatial functioning - Influence of participant's characteristics	Mathematical skills: - MILE group improved significantly more on total KeyMath score from pre-to post-testing compared to contrast group ($F(1, 27) = 5.89, p < 0.05, \eta 2 = 0.19$); - MILE group gained significantly more raw points on the Basic Concepts composite than contrast group ($F(1, 27) = 4.98, p < 0.05, \eta 2 = 0.16$) but the overall MANOVA of the 5 subtests of the Basic Concepts composite was not significant ($F(5, 27) = 2.01, p > 0.05$); - MILE group did not gain significantly more points on Operations and Problem Solving than contrast group; - MILE group showed greater increases in total math achievement than control group from pre-test to 6-months		- Post-testing by a blinded research assistant - Working Memory Test Battery for Children suitable for children aged 5-15 years - No assessment of executive functioning, working memory and visuospatial functioning at 6-months follow-up - N at follow-up: 19 - Possible effect of control intervention on outcomes - Possible practice effect - MILE group	Moderate (ROBINS-I)
	MILE: - Assigned: n = 15 - Received: n = 15 - Lost to immediate follow-up: n = 0 - Analysed (immediate): n = 15 - Lost to 6-months follow-up: n = 3 - Analysed (6-months): n = 12	SSIS: - Assigned: n = 13 - Received: n = 13 - Lost to immediate follow-up: n = 0 - Analysed (immediate): n = 13 - Lost to 6-months follow-up: n = 6 - Analysed (6-months): n = 7										

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								follow-up ($F(1, 18) = 5.47$, $p < 0.05$, $\eta 2 = 0.24$) Executive functioning: No significant differences in raw scores on Auditory Attention and Response set, but trend: MILE group had larger gains in total correct in Auditory Attention ($p = 0.18$, total correct in Response ($p = 0.13$) and in Omission errors in Response ($p = 0.13$) compared to control group. Working Memory: No significant treatment effect Visuospatial functioning: No significant treatment effect Influence of participant's characteristics: - Within the MILE group: Older age was associated with higher KeyMath Total and Operations raw change scores. PAE 'diagnosis' was strongly associated with greater raw point gains in Operations, Problem Solving, and Total Score. A lower Verbal IQ was associated with greater	had lower Math scores at pre-test (greater improvement potential)	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								change in KeyMath Operations and Problem Solving raw scores. A strong negative relationship was observed between overall IQ and KeyMath Problem Solving raw change score ($r(13) = -0.54, p < 0.05$). Sex was not significantly related to KeyMath Total raw change score. SES was not significantly correlated with changes in math achievement - Within the SSIS group: PAE 'diagnosis' was not associated with greater raw point gains in Operations, Problem Solving, and Total Score. A higher Verbal and Visual IQ was associated with more raw changes in Problem Solving. IQ was strongly positively related to KeyMath Problem Solving raw change score ($r(11) = 0.85, p < 0.01$). Sex was not significantly		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								related to KeyMath Total raw change score. SES was not significantly correlated with changes in math achievement.		
Wells et al. (2012) (12) **RCT (rater-blinded)**	- Inclusion: confirmed PAE, FAS or ARND diagnosis - Exclusion: serious head trauma; current/historical lead poisoning; genetic/dysmorphic syndrome (other than FAS) - No exclusion: exposures to other drugs (marijuana/cocaine) - Age: 6–11 years - Eligible for enrolment: n = 90 - Enrolled: n = 78		NA		NHT: - Parents received feedback and recommendations regarding child's behaviour, learning and emotional functioning - Parent training: psychoeducation in group setting - Children's' training: - NHT: program in group setting teaching children to recognize individual deficits and to develop strategies to compensate for them (integration of techniques of therapy of traumatic brain injury, and Alert Program: analogy of car engine) - Conjoined parent and children training at the end of each session - Weekly 75-minute sessions for 12 weeks	Control: - Parents received feedback and recommendations regarding child's behaviour, learning and emotional functioning - No further intervention	- Executive functioning - Emotional and social problem-solving skills	Executive functioning: - Significant interaction between group and time, F(8, 57) = 3.09, p = 0.006, ηp2 = 0.30); significant main effect for group, F(8, 57) = 2.61, p = 0.02 with treatment group showing more improvement; nonsignificant main effect for time, F(8, 57) = 1.93, p = 0.07 - No specific subtest was responsible for the significant effect, but the combination of the subtests Emotional problem solving: - Significant interaction between group and time, F(7, 52) = 2.92, p = 0.012, ηp2 = 0.28; significant main effect for group, F(7, 52) = 3.54, p = 0.003 with treatment group showing	- Only children living with foster or adoptive caregivers - No predetermined allocation sequence for randomization, but randomization through random numbers - Transformation of the data to eliminate skewness by extreme outliers - Outcome differences might be muted by the extensive feedback and comprehensi	Moderate (RoB-2)
	Neurocognitive habilitation therapy (NHT): n = 40	Control: n = 38								

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							more improvement; and significant main effect of time, F(7, 52) = 492.88, p < 0.001 - Specific subtest was responsible for significant effect: treatment group did not rely on easy or unrealistic solutions to problems	ve recommendations the assessment psychologist provided to all	
Nash et al. (2015) (13) **CCT (not randomized)**	- Inclusion: Children with FASD diagnosis - Exclusion: IQ < IQ 70 - Age: 8-12 years TXT: - Assigned: n = 14 - Completed: n = 12 - Received: n = 15 - Analysed (immediate): n = 12 - Lost to 6-months follow-up: n = 3 - Analysed (6-months): n = 9	Delayed treatment control group (DTC): - Assigned: n = 15 - Completed: n = 13 - Received: n = 15 - Analysed (immediate): n = 13	No completion: n = 4 (3 children (1 TXT, 2 DTC) had custody access issues and did not continue after baseline testing; and 1 child was lost to follow-up between the initial screening interview and scheduling of baseline testing)	TXT: - Alert: Program targeting self-regulation skills through sensory integration and cognitive processing activities (analogy of a car engine) in three stages: awareness, self-regulation strategies, independent usage - 12 1-hour sessions for 14 weeks	DTC: Waiting list	- Cognitive executive functioning - Socio-affective executive functioning - Emotional / behavioural functioning - Social skills	- Significant improvements of TXT compared to DTC in inhabitation naming (F(2, 20) = 6.12, p = 0.001, effect size = 0.283) with scores changing into the normal range - No significant changes in Inhibition-Inhibition score (F(2, 18) = 3.27, p = 0.15, effect size = 0.060) or Inhibition-Switching (F(2, 18) = 2.12, p = 0.30, effect size = 0.010) in TXT compared to DTC For attention, trend-level effect for the TEA-Ch Score (F(2, 22) = 2.89, p = 0.15; effect size = 0.047) - No group differences in attention switching or	- Different tests for similar outcomes - did not reach significance - Differences in the groups regarding ADHD diagnosis, and alcohol and secondary drugs - No correction for comorbidities - Child with IQ = 70 did not master the third stage	Moderate (ROBINS-I)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							planning from CANTAB - Significant treatment effect for NEPSY Affect recognition ($F(2, 21) = 4.82$, $p = 0.05$, effect size = 0.103) with scores improving into the normal in TXT - For social cognition, trend level effect for Strategic Control of Emotions ($F(2, 21) = 6.49$, $p = 0.07$, effect size = 0.004) with TXT showing improvement and Personalized Emotions ($F(2, 21) = 5.46$, $p = 0.09$, effect size = 0.002) with DTC showing improvements - Sign. treatment effect in behavioural regulation ($F(2, 21) = 22.6$, $p = 0.01$, effect size = 0.189) and trend-level in General Executive Functioning ($F(2, 21) = 21.7$, $p = 0.06$, effect size = 0.103) with TXT showing improvements - Sign. treatment effect for Emotional control ($F(2, 21) = 4.29$, $p = 0.03$, effect size =		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
									0.170) with TXT showing improvements - Trend-level for Inhibition control (F(2, 21) = 1.96, p = 0.09, effect size =0 .085) and CBCL Externalizing Problems (F(2, 21) = 34.6, p = 0.08, effect size = 0.095) with TXT showing improvements - No treatment effects were observed for the CBCL Total Behaviour Problems or SSIS Social Skills scores. - Results from parent-questionnaire data obtained at 6-month follow-up in nine TXT cases revealed that treatment effects observed at first post-test were sustained after 6 months, while an improvement on the Inhibit subscale of the BRIEF was also noted (M post-test (SD): 78.9 (8.7); M follow-up (SD) 74.6 (10.6); p = 0.01)			
Soh et al. (2015	Treatment and waiting list group:		TXT: Before pre-	DTC: Before pre-	CT: After post-	TXT: - Alert: Program	DTC: waiting list	CT: no	- Emoti	Emotion regula	- 2 children	High (ROBI

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
) (14) CCT (not randomized)	- Inclusion: Children with FASD included in clinic files or children in FASD support groups - Exclusion: Head injury requiring hospitalization, other neurological abnormalities, a debilitating or chronic medical condition, contraindications to MRI (e.g. braces, other implanted metal devices) - No exclusion: ADHD Healthy control group: - Inclusion: Children without PAE, psychiatric diagnosis (e.g. ADHD) or learning disability In total: - Age: 8–12 years - Recruited: n = 65	test: n = 3 (drop-out: 1; refused scan:2) After pre-test: Drop-out: n = 1; refused scan: n = 1)	test: n = 1 (refused scan) After pre-test: n = 1 (movement) After post-test: n = 2 (movement)	test: n = 7 (undisclosed exposure: 1; low IQ/learning disability: 2, technical problems: 1; movement: 1; braces: 2) After post-test: n = 1 (movement)	targeting self-regulation skills through sensory integration and cognitive processing activities (analogy of a car engine) in three stages: awareness, self-regulation strategies, independent usage - 12 1,5-hour sessions for 14 weeks		intervention	on regulation - Inhibition - Brain structure and function	tion: BRIEF: significant group* time interaction with TXT having the largest improvement (p = 0.04) (TXT > CT > DTC) Inhibition: NEPSY-II: sign. group* time interaction in inhibition subscale with improvements in TXT and CT (p = 0.01) (CT, TX > DTC) Brain structure and function: MRI: - While controlling for multiple comparisons: no significant changes among groups - Uncorrected data	without FASD diagnosis in TXT - Only 1 childrn with FAS in DTC and no child in TXT - 1 family in TXT was reassignment to DTC after pre-test - No between and within group differences with false discovery rate applied (only uncorrected) - Large number of comparisons (possible false-positive/type 1 errors) - Group differences in time between pre- and post-testing (TXT > DTC > CT) - More females in DTC than TXT (differences in	NS-I)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								: Significant increase in grey matter volumes in some brain regions (e. g. related to self-regulation) in TXT compared to DTC (p between < 0.0001 and 0.005) - Increase in grey matter volume in TXT, DTC and CT in different areas (p between 0.0001 and 0.001) - TXT still differed from CT group	neuro developmental peaks) - Normal brain changes during this age - No examination of structure-function correlations on DTC and CT (placebo effect) - Mask was relatively large and allowed for a large number of voxel comparisons	

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results		Comments	Risk of Bias
									regarding neuroanatomy after treatment		
Coles et al. (2015) (15) **RCT**	- Inclusion: Children with PAE with significant levels of alcohol-related physical features or with a clinical diagnosis of FAS/pFAS - Age: 5–10 years - Recruited: 30 children	GoFAR: Drop-out: n = 3 (unknown)	FACELAND: Drop-out: n = 3 (family crisis: 2; unknown: 1)	Control: Drop-out: n = 1 (unknown)	GoFAR with 3 components: - Children: Children learn metacognitive control strategies (FAR methodology) through computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour analogue therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training)	FACELAND with 3 components: - Children: Children learn to identify emotions through a computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour analogue therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training)	Control: no intervention	Disruptive behaviour	- No overall time point effect, $F(5, 90) < 1$, but a significant treatment group*time point effect on the disruptive behaviour composite, $F(4, 36) = 2.903$, $p < 0.035$, $\eta p2 = 0.244$. - No time point differences in the Control - GoFAR had significan	- Maintenance of the behavioural change is unknown. - Generalisability to other situations is unknown. - Parents and observers were not blinded	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs			Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								t improvements in disruptive behaviour at Mid-Treatment after the Game learning - FACELAND had significant improvements in disruptive behaviour at Posttreatment, after completing the BAT sessions - Intent to treat analysis: trend for the treatment group*time point interaction, F(4, 42) = 1.823, p < 0.14		

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
						2, ηp2 = 0.148		
Coles et al. (2018) (16) **RCT**	- Inclusion: Children with PAE with significant levels of alcohol-related physical features or with a clinical diagnosis of FAS/pFAS - Parents needed to attend a group workshop on the impact of PAE on neurodevelopmental functioning before enrolment - Age: 5–10 years - Recruited: n = 30 - Completed: n = 25	NA	GoFAR with 3 components: - Children: Children learn metacognitive control strategies (FAR methodology) through computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour analog therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training)	FACELAND with 3 components - Children: Children learn to identify emotions through a computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour	Control: no intervention	- Neurocognition - Adaptive functioning - Behaviour - Parents' satisfaction and fidelity to treatment protocol	Neurocognition (attention regulation): - Only GoFAR showed significant improvements in summary score of TOVA = Attention Performance Index (API) that measures efficiency in sustaining attention and inhibiting impulsive responding. On this measure, children who received the GoFAR intervention showed significant improvement at Post Test while the other two groups did not (Wald $\chi(2) = 6.09$, $p < 0.05$) - Control group performed significantly better in NEPSY-Auditory Attention-SS than intervention groups Adaptive functioning: FACELAND and GoFAR had significant improvements in the Vineland Daily Living Skills, Domestic subscale that reflects adaptive	- Highly motivated parents - Child with intellectual disability (IQ < 60) could not complete the neurocognitive measures; others completed only some sessions. - Parents were not blinded (VABS, CBQ) - No bias with TOVA (computerized measures) - Both intervention groups had higher TOVA API at baseline compared to controls (possible ceiling effect)	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes		Results	Comments	Risk of Bias
				analogue therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training)			functioning in the home (in contrast to control) (Wald χ (1) =5.39, p < 0.02) Behaviour: On the CBQ, which measures Temperamental Functioning, Fear, one of the elements of Negative Affect was significantly reduced both when the three groups are compared (Wald χ (2) = 8.59, p < 0.01) and when both intervention groups were combined (Wald χ (1) = 7.91, p < 0.005) Fidelity: - Significant improvements in parent fidelity in carrying out the FAR methodology in FACELAND and GoFAR group (F(4, 13) = 8.0, p < 0.002, eta2 = 0.71) - Parent thought the program was helpful and would recommend it.		
Kable et al. (2016) (17) **RCT**	- Inclusion: Children with PAE with significant levels of alcohol-related physical features or with a clinical diagnosis of FAS/pFAS - Parents needed to attend a group workshop on the impact of PAE on neurodevelopmental functioning before enrolment - Age: 5–10 years - Recruited: n = 30 GoFAR - Assigned: n = 10 - Complet FACELAND - Assigned: n = 10 - Complet Control - Assign	FACELAND: re-initiation after 8 months due to family crisis: n = 1	GoFAR with 2 components: - Children: Children learn metacognitive control strategies (FAR methodology) through computer game (5 weekly sessions) - Parents: Parents learn about the	FACELAND with 2 components - Children: Children learn to identify emotions throug	Control: no intervention	- Impact of parental engagement in the learning program on child's	Impact of parental engagement in the learning program on child's self-regulation skills: - Child's ability to regulate attention was significantly related to therapist's	- Highly motivated parents - Parents were not blinded (parents questionnaire for disrup	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention	Control		Outcomes	Results	Comments	Risk of Bias
	ed: n = 9 - Analysed: n = 9	ed: n = 9 - Analysed: n = 10	ed: n = 10 - Completed: n = 9 - Analysed: n = 9		neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions)	h a computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to childrn's sessions)		self-regulation skills - Disruptive behaviour	ratings of achievement of therapy goals (r = −0.70, p < 0.001) - Trend: Child's ability to regulate attention was correlated with parental completion of homework (r = −0.44, p = 0.059) - Trend between therapist's ratings of parent's achievement of therapy goals and reduction in children's destructive behaviour (r = 0.39, p = 0.10) Disruptive behaviour: - No significant multivariate group effect, F(12, 42) = 1.58, p = 0.134, η2 = 0.311 - Trend for a specific univariate effect on change in sustained mental effort, F(2, 25) = 2.77, p = 0.08, η2 = 0.181 - GoFAR had a significant reduction in frustration level relative to individuals in FACELAND and Controls, p = 0.05, and a trend was found for those in GoFAR making	tive behaviour)	

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
						more improvement in sustained mental effort, p = 0.09. Contrasts between those in FACELAND and Controls were not significant. - GoFAR demonstrated greater reductions on disruptive behavioural outcomes than FACELAND on change in sustained mental effort F(1, 17) = 5.85, p = 0.027, η2 = 0.26 (but not a significant multivariate group effect).		
Petrenko et al. (2017) (18) **RCT**	- Inclusion: FASD diagnosis or confirmed PAE; 4-8 years old; living within a reasonable distance of two New York study sites; expected to remain in their current placement for the study duration (∼18 months, including 9-month intervention and follow-up time points) - Exclusion: moderate to severe intellectual disabilities (IQ < 55); lacked sufficient English proficiency; severe physical or mental conditions - Age: 4–8 years FoT: - Assigned: n = 19 - Accepted: n = 16 - Completed: n = 15 - Analysed: n = 15 Control: - Assigned: n = 11 - Accepted: n = 10 - Completed: n = 9 - Analysed: n = 12 (3 declining treatment were included in analysis)	FoT: 3 families declining treatment (logistical difficulties)	FoT: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to caregivers) FoT including 2 empirically-validated programs: - The preschool/ kindergarten Promoting Alternative Thinking Strategies (PATHS) curriculum (Domitrovich et al., 2005): Program in	Control: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to caregivers)	- Satisfaction with FoT - Child's emotional and behavioural functioning - Child's impairment - Child's self-perception and environment - Child's behavioural problems - Parental knowledge and advocacy - Families' needs met - Parenting strategies and parental attributions for child misbehavi	Satisfaction with FoT: - CSQ: high satisfaction - PEI-FOT: high level of enjoyment; felt that they could apply what they learned; good relationship with their FMF Specialist; felt the Specialist understood their feelings and problems; children generally looked forward to coming to group; and learned new skills; children had relatively more difficulty	- Families were not precluded from participating in other intervention programs. - Fidelity was monitored in weekly individual/group supervision - Attempts were made for blinding research assista	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
				small groups including children with and without PAE and aiming at preventing violence, aggression, and other behavioural problems by promoting social competence and developing emotional skills. Children learn self-control, emotional understanding, positive self-esteem, peer relationships, and interpersonal problem solving skills - The Families Moving Forward (FMF) Program (Bertrand, 2009): Core sessions for parents in groups aiming at creating a stable home to reduce violence by targeting family-level risk and protective factors		our - Efficacy in parenting role and satisfaction with parenting role: - Perceives support from family, friends, significant others, and involved professionals - Change in self-care - Stress in parent-child system	applying what they learned Child's emotional and behavioural regulation: ERC: - Emotion regulation: significant group difference: parents reported a change in child emotion regulation (ERC d_{ppc} = 1.18). This effect reflected a medium to large improvement in emotion regulation for the intervention group and medium-sized decrement for the comparison group. - Negative affect: main effect of time Child's impairment: IRS: medium to large group effect size for parent-reported self-esteem was found (IRS self-esteem d_{ppc} = 0.77), which was not statistically different between groups. (significant effect of time p = 0.046); main effect of time for global impairment Child's self-perception and environment: BPI: medium	nt to intervention condition at assessment points - Small sample size => powered to detect only large effects - Effect sizes are resistant to sample size influence and give a truer measure of the magnitude of effects. - 3 families declined intervention for logistical reasons and were combined with control group in analyses - All caregivers completed one individualized session; 12 completed 2 individualized sessions; 11	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							to large group effect was found for child-reported anxiety symptoms (BPI Overanxious d_{ppc} = 0.75), which did not reach statistical significance. FoT had a higher level of anxiety symptoms at pre-intervention with improvement over time (d within = 0.80) Controls had a minimal change in self-reported anxiety. Main effect of time for child report of prosocial skills and conduct problems Child's behavioural problems: ECBI: Main effect of time for parental report of child disruptive behaviour Parental knowledge and advocacy: K&A: statistically significant between-group difference: large effect size for knowledge and advocacy with FoT improving (K&A d_{ppc} = 1.02) Families' needs met: FNM: significant between group difference: large effect with FoT improving	completed the school consultation - Children in both groups declined in their self-esteem. FoT may have buffered this decline. - Highly motivated families - Some families had logistical reasons not to participate in intervention - Lack of objective data (parental reports) - Findings could be due to the more intensive care with FoT compared to controls	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							(d_{ppc} = 0.72) No statistical significance: - Parenting strategies and parental attributions for child misbehaviour - Efficacy in parenting role and satisfaction with parenting role - Perceives support from family, friends, significant others, and involved professionals - Change in self-care - Stress in parent-child system		
Petrenko et al. (2019) (19) **RCT**	- Inclusion: FASD diagnosis or confirmed PAE; 4-8 years old; living within a reasonable distance of two New York study sites; expected to remain in their current placement for the study duration (∼18 months, including 9-month intervention and follow-up time points) - Exclusion: moderate to severe intellectual disabilities (IQ < 55); lacked sufficient English proficiency; severe physical or mental conditions - Age: 4–8 years FoT: Initial trial: - Assigned: n = 19 - Accepted: n = 16 - Completed: n = 15 - Analysed: n = 15 Follow-up:	Control: Initial trial: - Assigned: n = 11 - Accepted: n = 10 - Completed: n = 9 - Analysed: n = 12 (3 declining treatment were included in analysis)	Follow-up: n = 3 (change in child placement (n = 1); loss of contact (n = 1); declining to participate due to time demands of other services (n = 1))	FoT: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to caregivers) FoT including 2 empirically-validated programs: - The preschool/ kindergarten Promoting Alternative Thinking Strategies (PATHS) curriculum (Domitrovich et al., 2005): Program in small groups including children with	Control: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to caregivers)	6 months sustainability of: - Child's emotional and behavioural functioning - Child's impairment - Child's self-perception and environment - Child's behavioural problems - Parental knowledge and advocacy - Families' needs met - Parenting strategies and parental attributions for child misbehaviour - Efficacy in	Child's emotional and behavioural regulation: ERC: - Emotion regulation: FoT had medium-large improvements during intervention and declined in follow-up (remained above baseline-levels) (d within = -0.56); controls had a moderate worsening during the study and improved in follow-up (slightly below baseline-levels) (d within = 0.38). Significant group*time	- Families were not precluded from participating in other intervention programs. - Fidelity was monitored in weekly individual/group supervision - Attempts were made for blinding research assistant to intervention	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
	- Completed: n = 14 - Analysed: n = 14	Follow-up: - Completed: n = 10 - Analysed: n = 10		and without PAE and aiming at preventing violence, aggression, and other behavioural problems by promoting social competence and developing emotional skills. Children learn self-control, emotional understanding, positive self-esteem, peer relationships, and interpersonal problem solving skills - The Families Moving Forward (FMF) Program (Bertrand, 2009): Core sessions for parents in groups aiming at creating a stable home to reduce violence by targeting family-level risk and protective factors		parenting role and satisfaction with parenting role: - Perceives support from family, friends, significant others, and involved professionals - Change in self-care - Stress in parent-child system	effect: changes in emotion regulation over time differed significantly by treatment group (F(2, 44) = 8.032, p = 0.001) - Negative affect: FoT had a small-medium improvement during intervention and an additional minimal-small improvement in follow-up (d within = 0.15); controls had a minimal improvement during study and a small improvement in follow-up (d within = 0.24), both groups had a similar magnitude of change. Significant time effect: significantly higher levels of negative affect at baseline than at 6-month follow-up (F(2, 44) = 4.68, p = 0.014), no significant group or group*time effect Child's impairment: IRS: FoT remained stable during intervention and had a moderate decrease in follow-up (d within = -0.41); controls	condition at assessment points - Small sample size => powered to detect only large effects - Effect sizes are resistant to sample size influence and give a truer measure of the magnitude of effects. - 3 families declined intervention for logistical reasons and were combined with control group in analyses - All caregivers completed one individualized session; 12 completed 2 individualized sessions; 11 completed the	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							had a medium-large decline during study and a minimal decline in follow-up (d within = -0.10). Significant time effect: F(2, 38) = 10.07, p = 0.018), no significant group or group*time effect. Both groups had a decline in self-esteem Child's behavioural problems: ECBI: FoT group moderately decrease in behavioural intensity during the course of the intervention and maintained this change over the 6-month follow-up interval (d within = 0). Children in the comparison group, who had a small decrease in behavioural intensity during the intervention time, had an additional small decrease in intensity of behaviour problems during last 6 months (d within = -0.25). When considering overall change from baseline to follow-up, effect size analysis showed negligible group difference	school consultation - Children in both groups declined in their self-esteem. FoT may have buffered this decline. - Highly motivated families - Some families had logistical reasons not to participate in intervention Follow-up: - Lack of objective data (parental reports) - 3 participants completed the follow-up measures at home - The decline in families' needs met could be due to an increase in needs as childre	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							(d_{ppc} = 0.03). Significant time effect, with the most intense behaviours at baseline, significantly less intense behaviours at post-intervention, and significantly less intense behaviours at 6-month follow-up ($F(2, 44) = 16.77$, $p < 0.001$) on average across groups. No significant main effect for group and no significant group*time interaction. Parental knowledge and advocacy: K&A: FoT had large gains during intervention and maintained them in follow-up; controls had approximately the same level across all time points. Significant main effect of time; no group effect; significant group*time effect ($F(2, 40) = 3.241$, $p < 0.050$), with families in the intervention group reporting significantly less knowledge at baseline (M = 26.50) compared to post-intervention (M = 31.00) and 6-month follow-up (M = 31.21)) Families' needs met:	n progress in early school years - Data collection at different time points: baseline (summer), post-test (summer), follow-up (winter) - No intent-to-treat analyses => results could overestimate the treatment effect	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							FNM: FoT had a large increase in needs met during intervention and had a large decline (d within = -1.03) in the follow-up (remained above baseline-level and reflected an overall medium level improvement (d within = 0.55)); controls had a small-medium increase during study and a large decline (d within = -1.03) in follow-up (below baseline-level (d within = -0.60)). The overall group effect across the length of the study was large (d_{ppc} = 1.07), and favoured the intervention group (M = 3.2) as compared to the comparison group (M = 2.8; F(1, 20) = 4.682, p = 0.043). Main effect for time: scores for FNM were significantly higher for both groups immediately post-intervention (M = 3.37) than they were at baseline (M = 2.84) or follow-up (M = 2.79; F(2, 40) = 6.78, p = 0.003). Significant group*time interaction (F(2, 40) = 2.90, p = 0.067) with		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							FoT reporting that their needs were better met post-intervention (M = 3.62) compared to baseline (M = 2.81), and the comparison group reporting their needs were better met post-intervention (M = 3.13) compared follow-up (M = 2.41). Efficacy in parenting role and satisfaction with parenting role - PSOC: Parenting self-efficacy: FoT had a small-medium improvement during study and an additional small-medium improvement (d within = 0.34) in follow-up; controls had a minimal change during study and a small-medium worsening (d within = -0.39) in follow-up. large group effect in follow-up (d_{ppc} = 1.14 => large effect size), favouring FoT . Changes in efficacy over time significantly differed by treatment group (F(2, 44) = 3.51, p = 0.038)		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							- Parenting satisfaction: FoT had a medium improvement during intervention and a small-medium worsening (d within = -0.37) in follow-up (remaining above baseline); controls had a minimal change during study and a moderate improvement (d within = 0.52) in follow-up (similar level to FoT post-intervention). Significant group*time interaction, with parenting satisfaction in the comparison group significantly higher at follow-up (M = 38.3) than at baseline (M = 34.6) or post-intervention (M = 34.3; F(2, 44) = 3.48, p = 0.039). Small-moderate group difference favouring the comparison group (d_{ppc} = -0.38) Stress in parent-child system PSI: both groups had minimal-small changes in distress across each time point; FoT had		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							minimal-small improvements (d within = -0.11) in follow-up; controls had minimal-small worsening (d within = 0.13) in follow-up. Small group effect at follow-up compared to baseline (d_{ppc} = 0.21), no significant time effect, no significant group or group*time effect Outcomes meeting statistical significance (treatment x group: $p < 0.05$) or practical significance (d_{ppc} = 0.41): - Parents' outcomes: self-efficacy (p = 0.039; dpcc = 1.14), family needs met (p = 0.067; dpcc = 0.67), FASD knowledge (p = 0.050; dpcc = 0.60), parenting satisfaction (p = 0.038; dpcc = -0.38). - Children's outcomes: emotion regulation (p = 0.001; dpcc = 0.30), self-esteem (p = 0.294; dpcc = 0.56).		
O'Connor et al. (2016) (20) **RCT**	- Inclusion: Composite IQ ≥ 70; English speaking; living with at least 1 custodial parent/guardian; history of PAE - Exclusion: diagnosis of intellectual disability; psychotic disorder, pervasive developmental disorder - Age: 13–18 years		SUI: Drop-out: n = 2 (conflicting obligation)	SUI with 2 components (parallel; each b = 6; weekly 1-hour sessions in small groups): - Adolescents: Modified version of an empirically	Control: Adolescents and caregivers got written materials on alcohol misuse and stress	- Prevention and reduction of alcohol-related negative outcomes - Determination of possible	Prevention and reduction of alcohol-related negative outcomes: - Light/ moderate drinkers (post-	- Trained and qualified group leaders, standardized manua	Moderate (RoB-2)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
	- Recruited: n = 83 - Eligible after screening: n = 56 - Analysed: n = 54			validated procedure. The used strategies are focussed on modelling, coaching, behavioural rehearsal, and performance feedback; intervention incorporated motivational enhancement techniques, normative feedback, education, risk assessment, coping and alcohol refusal skills training. Participants got a Workbook. - Caregivers: Adapted from the NIAAA protocol "Make a Difference: Talk to Your Child About Alcohol". The aim was to empower them in assisting their teens to resist alcohol use. Caregivers got a workbook, as well.	reduction.	increase in alcohol risk in abstinent youths - Satisfaction of SUI	intervention): significant treatment effects, with SUI having significantly lower levels of alcohol risk and fewer negative behaviours than controls: AUDIT (F(1, 15) = 5.43, p = 0.03, d = 1.08) and RAPI (F(1, 15) = 8.60, p = 0.01, d = 0.99). No significant differences in CRAFFT. - Light/ moderate drinkers (Follow-up): Gains in RAPI sustained (F(1, 15) = 4.53, p = 0.05, d = 0.83). Gains in AUDIT reached a nonsignificant large effect size (d = 0.76) Determination of possible increase in alcohol risk in abstinent youths: No group differences at baseline; no differences or change in outcome variables at post-test or at 3 months follow-up Satisfaction of SUI: - Adolescents: 96 % reported to be confident at avoiding risky situations based upon what they have learned; 92	ls, ongoing weekly supervision, live monitoring of sessions.; fidelity rating ≥ 95 % - No detailed definition of drinker-type; no heavy drinker-type classification - No significant differences in CRAFFT might be due to low occurrence of behaviours measured in CRAFFT - Motivated caregivers who actively seeked help - Impact of caregivers has not been assessed - Impact of age has not been analysed (large age	
	Project Step up (SUI): - Assigned: n = 28 - Analysed: n = 26 - Abstinent/ infrequent drinkers: n = 15 - Light/ moderate drinkers: b = 11	Control: - Assigned: n = 28 - Analysed: n = 28 - Abstinent/ infrequent drinkers: n = 21 - Light/ moderate drinkers: b = 7							

<table>
<tr><th>Reference Study Type</th><th colspan="4">Participants (Number and Characteristics)</th><th>Drop-outs</th><th colspan="2">Intervention</th><th>Control</th><th>Outcomes</th><th>Results</th><th>Comments</th><th>Risk of Bias</th></tr>
<tr><td></td><td colspan="4"></td><td></td><td colspan="2"></td><td></td><td></td><td>% reported the program to be helpful
- Caregivers: 96 % stated that they believe the program help the teens to make better choices regarding alcohol; 96 % reported to be satisfied</td><td>range)</td><td></td></tr>
<tr><td>Jirikowic et al. (2016) (21)

CCT (not randomized)</td><td colspan="4">- Inclusion: confirmed PAE; diagnosis of FASD (FAS, SE-AE or ARND); a previously identified sensorimotor impairment based on clinical diagnostic assessment results.
- Exclusion: IQ < 60; a severe, co-occurring neuromotor condition that impaired ambulation/independent standing for at least 2 minutes; a history of serious head injury/seizures; a visual acuity impairment not corrected by glasses; report of any lower limb or back injury within the previous 6 months; current living in an unstable home placement.
- Age: 8–15 years</td><td>STABLE home:

3 children received equipment but never started; 2 started but did not finished due to frustration or dizziness; 1 finished but did not complete post-intervention assessments</td><td colspan="2">STABEL:
Virtual reality game (STABEL) that facilitates task-specific balance practice under altered sensory conditions (visual, vestibular, somatosensory) by moving on a pliable standing surface. Training consisted of 3 6-minute blocks that progressed in difficulty by altering stability and complexity of the VR visual display. Total of 5 30–35 minute sessions over 1 month.</td><td>Control:
No intervention</td><td>- Effectiveness of STABEL on balance and motor performance
- Feasibility in laboratory and home setting</td><td>Motor skills MABC-2:
- Balance standard score: no significant interaction, but significant differences by session (p = 0.02) and group (p = 0.04); home group had significant improvements compared to controls (p = 0.01); home and lab group (together) had significant improvements from pre-test to 1 week (p = 0.004), but no significant improvements from pre-test (p = 0.09) or 1 week (p = 0.11) to 1 month
- Total Motor standard score: significant interaction (p = 0.05); significant differences by session; home and lab group</td><td>- P-CTSIB-2 only suitable for children aged 6-12 years
- Small dose of STABEL
- No randomization
- No control for fidelity in home group and for other parallel interventions
- Possible ceiling effect might explain no detected changes in dynamic balance
- Pre- and 1-week-test differences</td><td>High

(ROBINS-I)</td></tr>
<tr><td></td><td>University laboratory (STABEL lab):
- Enrolled: n = 6
- Completed: n = 6
- Analysed: n = 6</td><td>Home (STABEL home):
- Enrolled: n = 15
- Completed: n = 9
- Analysed: n = 9</td><td>Control:
- Enrolled: n = 8
- Completed: n = 8
- Analysed: n = 8</td><td></td><td></td><td>STABEL lab:
Participants used STABEL in an university laboratory</td><td>STABEL home:
Participants used STABEL at home</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
									(together) had significant improvements from pre-test to 1 week, and pre-test to 1 month, but not from 1 week to 1 month Dynamic balance: DGI: no significant differences across time or between groups Static balance: P-CTSIB-2: Total Sensory Score: significant interactions (p = 0.02) and significant improvements for home STABEL compared to controls (p = 0.01); trends show higher post-intervention scores for lab and home groups	were beyond the error of the MABC-2 test, at a level that also suggests potential clinical significance - Lab group did not show significant improvements in any test compared to controls - Home group had overall milder CNS dysfunction based on their FASD diagnosis; lab group had more muscular weakness and - 1/3 who agreed to the home intervention did not complete training protocol due to unknown reason	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								s, frustration or dizziness	
McCoy et al. (2015) (22) **Uncontrolled intervention study**	- Children with FASD: Inclusion criteria: 8-16 years; confirmed PAE; FASD diagnosis; previously identified sensorimotor impairment based on clinical diagnostic assessment results - Exclusion: IQ < 60; severe co-occurring neuromotor condition that impaired ambulation or independent standing for ≥ 2 minutes; history of serious head injury/seizures; visual acuity impairment not corrected by glasses; report of any lower limb or back injury within the previous 6 months; currently living in an unstable home placement - Age: 8–16 years - Received: n = 11 - Completed: n = 11 - Analysed: n = 11	- Typically developed children (TD): - Inclusion: 8-16 years - Exclusion: identified sensory/motor impairment; current/past special education services; history of serious head injury/seizures; PAE (> 3 reported drinks by mother for the duration of pregnancy); visual acuity impairment not corrected by glasses; report of any lower limb or back injury within the previous 6 months - Age: 8–16 years Received: n = 11 - Completed: n = 11 - Analysed: n = 11	NA	STABEL: Virtual reality game (STABEL) that facilitates task-specific balance practice under altered sensory conditions (visual, vestibular, somatosensory) by moving on a pliable standing surface. Training consisted of 3 6-minute blocks that progressed in difficulty by altering stability and complexity of the VR visual display for a total of 30 minutes.	NA	- Feasibility of STABEL - Immediate effect on sensory attention and postural control	Feasibility: all participants interacted with STABEL and completed all training blocks For FASD children: 1. block: - fun: 82 % had fun, 18 % felt ok, 0 % had no fun - dizziness: 0 % felt dizzy, 18 % felt a little dizzy, 82 % had no dizziness 2. block: - fun: 100 % had fun - dizziness: 9 % felt dizzy, 9 % felt a little dizzy, 82 % had no dizziness 3. block: - fun: 55 % had fun, 18 % felt ok, 27 % had no fun - dizziness: 18 % felt dizzy, 0 % felt a little dizzy, 82 % had no dizziness For all children: Postural control: - No significant interactions for ellipse area of body sway or velocity outcomes - Significantly higher medial-lateral and anterior-posterior RMS	- Dizziness did not persist - Different exclusion criteria for FASD and TD childrен (TD childrен might have other diagnoses) - Examiner was not blinded for FASD or TD - α = 0,1 - Decreased postural stability could be due to fatigue (long testing sessions of 2.5h) - One-time practice with STABEL might be not enough to change sensory attention fractions - Body sway without any	Low (ROBINS-I modified)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
							velocities in post STABEL in most conditions in both groups (p = < 0.01 to 0.05) - No significant differences in ellipse area of body sway pre- compared to post-testing or FASD compared to TD. Sensory attention: - Entrainment gain: LLM = visual screen gain and tilt board gain increased significantly from pre- to post-testing only in TD (p = 0.08); LLL (p = 0.06) and LLH (p = 0.09) = significantly higher touch pole entrainment gain in both groups in post-testing; LLH = significantly higher visual screen gain in both groups in post-testing (p = 0.02); HHL = significantly lower touch pole gain in post-testing (p = 0.02) - SAF: No significant interaction or pre/post differences	extra sensory stimulation has not been measured - Measures of balance and functional motor performance have not been included to complement kinematic measures of sensory attention and postural control	
Zarnegar et al.	- Inclusion: age of ≤5 years, in the care of their adopted families for 6 months,		NA	The Neurosequential Model of	NA	- Children's developmental skills	Baseline: all children had clinically	- Therapists were	NI (ROBINS-I

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
(2016) (23) Uncontrolled intervention study	diagnosis of FASD by a medical provider, history of maltreatment or loss, adoptive caregiver(s) who could fully engage in the intervention process during the study time period and who could complete measures in English - Exclusion: taking of psychotropic medications, additional genetic syndrome, active grand-mal epileptic seizures, history of serious head injury, profound intellectual disability - Age: 10–53 months - Agreed to participate: n = 38 - Assigned: n = 15 - Excluded before treatment: n = 5 (missed appointments: 3; movement: 2) - Excluded after treatment: n = 3 (movement: 1; other familial reasons: 2) - Completed for at least 6 months: n = 10 - Analysed: N = 10 children and 20 adoptive parents		Therapeutics (NMT) Metrics were used to estimate the child's functional capacity. Based on that individual somatosensory interventions were suggested for each child. Additionally to somatosensory interventions: - Child-Parent Psychotherapy (CPP): evidence-based, relationship-focused, reflective, and developmentally oriented model of psychotherapy that uses caregivers as the agents of change. Weekly for 6 months. - Mindful Parenting Education (MPE): Parents received psychoeducation regarding FASD, their child's self-regulation and on how to work through their own feelings and emotions while dealing with them. Twice per week for 6 months.		- Children's functional capacity - Parental skills - Parental stress	significant deficits in all 4 functional domains in the CMR; all parents had clinically significant parenting stress Children's developmental skill: BBDI-2 Total Score: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 0.205 [0.148, 0.261]; Post-mean and 95 % CI: 0.518 [0.394, 0.641]; Standard error: 9.80; Standardized test statistic: 2.81; r (rank-biserial correlation): 0.63; p: 0.005*) Children's functional capacity: - NMT Total Score: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 23.40 [18.56, 28.24); Post-mean and 95 % CI: 45.20 [40.88, 49.52]; Standard error: 9.79; Standardized test statistic: 2.81; r (rank-biserial correlation): 0.64; p:	under the supervision of a licensed paediatric psychologist who was trained in CPP, Mindful Parenting, and NMT - Significant amount of families did not complete intervention (unknown reasons) - Improvements observed by multiple reporters: clinicians, parents - Possible effect of time - Different somatosensory interventions for each child - Unknown impact of CPP, MPE and NMT	modified)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
						0.005*) - NMT Cortical Modulation Ratio: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 0.205 [0.148, 0.261]; Post-mean and 95 % CI: 0.518 [0.394, 0.641]; Standard error: 9.80; Standardized test statistic: 2.81; r (rank-biserial correlation): 0.63; p 0.005*) Parental skills: Satisfaction survey: 18 reported an improvement in different areas of parental skills. Parental stress: PSI-SF Total Score: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 23.40 [18.56, 28.24; Post-mean and 95 % CI:] 45.20 [40.88, 49.52]; Standard error: 9.79; Standardized test statistic −2.81; r (rank-biserial correlation): −0.63; p: 0.005*)	alone - Very short evaluation window (unknown long-term effects)	
Rege	- Inclusion: PAE or FASD, 4–10	NA	SSIS-IG:	MILE:	- Social	Social skills	- Inclusi	Low

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
hr (2015) (24) **CCT (not randomized)**	years old - Exclusion: significant neurological or medical condition that would prevent them from benefiting from the interventions (e.g. autism) - Age: 4–10 years - Enrolled: n = 29			- Individual program that focusses on instruction, modelling, rehearsal, and performance feedback on social skills difficulties and in problem behaviours. - One-on-one instruction - 30 min. sessions, 1–2 times a week over 5–7 weeks (total of 5 hours)	- Individualized program that is based on specific math deficits and learning needs. - One-on-one-instruction - 30 min. sessions, 1–2 times a week over 5–7 weeks (total of 5 hours)	skills and competing problem behaviours - Social, emotional and behavioural problem areas	and competing problem behaviours SSIS-RS: - No significant impact of SSIS-IG on the SSIS-RS composite scores social skills F(1, 26) = 0.016, p = 0.90; problem behaviours F(1, 26) = 2.81, p = 0.12 relative MILE. - Analysing differences between participants pre- and post-test SSIS-RS scores separately within each intervention (paired-sample t tests): SSIS-IG improved significantly on problem behaviour scale (decrease by 8.6 standard points; t(13)= 2.52, p = 0.03) compared to MILE (decrease by 1.7; t(13) = 0.76, p = 0.46). Social, emotional and behavioural problem areas CBCL: Social composite approached significance F(1, 21) = 3.4, p= 0.08; however it did not approach significance for the social problems subtest F(1, 21)= 0.54, p= 0.47.	on of children with ADHD or ODD - Groups not randomized but matched by age, diagnosis, IQ and gender - Group assignment after pre-tests - Families with two children in the study were allowed to have both children in the same group (sibling pairs N = 2). - Post-tests by a blinded research assistant - SSIS-IG: normally in group setting - Caregivers who are able to have their child participate in a study may	(ROBINS-I)
	The Social Skills Improvement System Intervention Guide (SSIS-IG): - Assigned: n = 14 - Completed: n = 14 - Analysed: n = 14	MILE: - Assigned: n = 15 - Completed: n = 15 - Analysed: n = 14							

Reference Study Type	Participants (Number and Characteristics)		Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								also be more likely to connect their children with various social activities. - Possible impact of individualized attention from researchers on problem behaviour (both groups) - Unknown long-term effects - Possible impact of MILE on social skills - Possible mismatch between the degree of each type of deficit targeted within SSIS and children's social skills impairments - Baseline: all children in the clinical	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
									range and significantly different than the normative mean on social skills, the Externalizing Problem scale and Total Problems scale - Improvements of SSIS-IG on problem behaviour cannot be exclusively attributed to the intervention - CBCL social scales were only available for participants ≥ 5 (N for each group = 12).	
O'Connor et al. (2012) (25) **CCT (not randomized)**	- Families were required to complete 2 intake sessions with a Child and Family Guidance Centre clinician (assessment and treatment planning session) - Inclusion criteria for children: 6-12 years of age; IQ ≥ 70; English speaking; living with at least 1 custodial parent or guardian; with/without PAE - Inclusion criteria for parents: English or Spanish speaking - Exclusion criteria for children: major sensory or motor		CFT n = 9 Reasons for not receiving intervention: child illness, family circumstances, child unsafe, unknown	SOC: n = 9 Reasons for not receiving intervention: child illness, family circumstances, child unsafe,	Modified CFT with 2 components: - Children training in group setting to emphasize the child's friendship skills. It is tailored to the neurodevelopmental needs of children	SOC: - Children training in group sessions that were process-oriented and behaviourally based, involving group	- Knowledge of social skills - Child self-concept - Overall social skills - Behaviour problems (parent-report) - Comparison between children	Knowledge of social skills: TSSK: Significant condition effect, with CFT showing significantly improved knowledge of appropriate social skills compared to SOC, $F(1, 62) = 21.34$, $p <$	- Possible impact of involvement of parents in the program on subjective outco	Moderate (ROBINS-I)

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
	deficits; past diagnosis of intellectual disability, psychotic disorder, pervasive developmental disorder - Age: 6–12 years - Recruited: 85 children (with PAE = 32; without PAE = 53)			unknown	with FASD. Social skills were taught using instruction on simple rules of social behaviour, modelling, behavioural rehearsal, and performance feedback through coaching during treatment sessions. 12 90-minute sessions over the course of 12 weeks. - Parents training in separate concurrent sessions in group setting to learn the key skills being taught to their children. They were taught how to facilitate social competence in their children by arranging play dates, facilitating completion of weekly homework assignments, and providing in vivo social coaching. Handouts outlining the skills being taught to children are distributed to parents. 12 90-minute sessions over the course of 12 weeks.	discussion and cooperative projects. Training involved discussion and practice of rules of social behaviour typically thought important by adults, but not necessarily empirically demonstrated to be predictive of peer acceptance nor often practiced by socially skilled children in naturalistic settings. 12 90-minute sessions over the course of 12 weeks. - No parent training	with and without FASD	0.0001, d = 1.22 (95 % CI (0.69, 1.73)); F^2 = 0.34 (95 % CI (0.09, 0.90)). No other significant main or interaction effects. Child self-concept: Piers Harris 2: Significant condition effect, with CFT showing significantly improved overall self-concept, F(1, 62) = 4.21, p < 0.05, especially on individual domains of self-concept, children reported improved behavioural adjustment F(1, 62) = 5.69, p < 0.02, d = 0.58 (95 % CI (0.09, 1.07)), F^2 = 0.09 (95 % CI (0.004, 0.36)); intellectual／school status, F(1, 62) = 6.01, p < 0.02, d = 0.39 (95 % CI (-0.10, 0.87)), F^2 = 0.10 (95 % CI (0.006, 0.34)); and freedom from anxiety, F(1, 62) = 7.63, p < 0.01,d = 0.70 (95 % CI (0.21, 1.19)), F^2 = 0.12 (95 % CI (0.008, 0.42)), compared to SOC. No significant improvement in physical appearance, F(1, 62) = 0.12, p = 0.73, popularity, F(1, 62) = 0.51, p = 0.48, or happiness and satisfaction,	me measures. - Children reported changes themselves - No independent evaluation of children's behaviour in a naturalistic setting - No child with FAS - Only families included of parents who actively seek help for their children and who were highly motivated to participate - 2 children were asked to leave the program because of significant disruptive behaviour (CFT and SOC) - Therapists in the SOC	
		Children's Friendship Training (CFT): - Assigned: n = 41 - Received: n = 32 - Analysed posttreatment: n = 32 - Analysed using multiple imputations: n = 41								
		Standard of care (SOC): - Assigned: n = 44 - Received: n = 35 - Analysed posttreatment: n = 35 - Analysed using multiple imputations: n = 44								

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								F(1, 62) = 1.85, p = 0.18. No other significant main or interaction effects. Overall social skills: SSRS-P: No significant condition effect in improvement of overall social skills, F(1, 62) = 2.37, p = 0.12 because the 2 groups differed on their pre-treatment social skills scores. Some children in the SOC group started out scoring higher than the children in the CFT group and actually demonstrated a significant decline in social skills according to parent report. The CFT group, while showing a significant 18 point improvement compared to the improvement of 4 points in the SOC group, did not differ from the SOC group after controlling for pre-treatment levels. Analyses of individual index scores revealed statistically significant condition effects for assertion, F(1, 62) = 4.04, p < 0.05, d = 0.18 (95 % CI (-0.31, 0.66)), F^2 = 0.07 (95 % CI (0.0009,	conditi on were provid ed weekly supervi sion by their supervi sors	

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								0.28)); and responsibility, $F(1, 62) = 4.53$, $p < 0.04$, $d = 0.16$ (95 % CI (-0.32, 0.64)), $F^2 = 0.07$ (95 % CI (0.001, 0.31)); in favour of the CFT condition over the SOC condition. Analyses of cooperation, $F(1, 62) = 0.30$, $p = 0.59$, and self-control, $F(1, 62) = 0.75$, $p = 0.39$, did not yield statistically significant effects. No other significant main or interaction effects. Parent satisfaction questionnaire: - 90.7 % in CFT and 68.6 % in SOC reported confidence in their children's ability to get along better with other children because of treatment ($p < 0.04$). - 87.5 % in the CFT and 57 % in SOC reported that they were confident that they were better able to help their children make and keep friends because of the treatment ($p < 0.007$). - Groups were comparable		

Reference Study Type	Participants (Number and Characteristics)		Drop-outs		Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								in their overall satisfaction with (p < 0.68). Overall, 93.7 % in CFT and 88.6 % in SOC reported being very satisfied or highly satisfied with the treatment. Therapist satisfaction questionnaire: In CFT, 84 % agreed that the treatment was helpful, 100 % agreed that their clients enjoyed treatment, 92 % agreed that they would like to see the program adopted permanently at Child and Family Guidance Centre and would continue to use it. Concerns: program was hard to integrate into busy schedules, more time needed Treatment is equally effective for children with and without PAE		
Leenaars et al. (2012) (26) **Retrospective cohort study**	- Inclusion: closed case files of families for which at least one post needs or goals measure was available; families with ≥ child with FASD (confirmed FASD diagnosis; children possibly having FASD, but - maternal drinking was not confirmed, children being suspected of having FASD, but had not yet been assessed) - Age: 1–23 years - Analysed: n = 186 families		NA		Coaching Families Program (CF) is a family goal-based mentoring program on an individual level. Mentors educate families about FASD, help them access resources, and engage them in	NA	- Individual needs - Goal attainment - Caregiver stress - Satisfaction	Individual needs and goal attainment: - Length of time in the program was significantly related to both needs (r = -0.27, P < 0.001) and goals (r =	- Self-referred recruitment - No control for quality of mentorship, participation	Moderate (ROBINS-I modified)

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
			successful advocacy.			0.22, P < 0.001) indicating that the longer families spent in the program, the greater their reduction in needs and achievement of goals. - Individual needs significantly decreased from pre- to post-program: F(1, 187) = 152.69, P < 0.001, ηp2 = 0.45 - Significant increase in goal achievement from pre- to post-program: F(1, 165) = 317.46, P < 0.001, ηp2 = 0.66 Caregiver stress: Significant decrease in overall levels of caregiver stress from pre- to post-program: F(1, 72) = 39.409, P < 0.001, ηp2 = 0.354 No gender or age effect. Satisfaction: - High satisfaction with the program (98 %) and willingness to participate again (99 %); 32.1 % of caregivers reported parenting and handling their child better, 28.2 % reported understandi	in other services, family variables, or comorbid disorders. - Many files were not included in the analyses as there were no post needs or goals measure available (possible bias)	

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								ng their child and/or FASD better, and 14.5 % reported feeling less stressed, having increased patience, and being more positive. 65.6 % reported that they had not experienced any problems with the program - Reported challenges: feeling that mentor did not understand what it was like to live with a child with FASD, difficulties collaborating with other services, and a need for longer-term support. 38.8 % reported that there was no need for improvement or were unsure.		
Graham et al. (2016) (27) **Intervention study**	- Inclusion: English as primary language, 8-12 years - Exclusion: other known causes of mental deficiency, adopted from abroad after age of 5, head injury involving loss of consciousness, physical or psychiatric conditions that prevented involvement - Exclusion for analyses: accuracy < 80 % in Flanker task; being an extreme outlier (at least 3 SD from group mean) across RT and accuracy in Flanker task - Age: 8–12 years			NA	Modified flanker task including reward (positive reinforcement) and response cost (negative punishment): 4 blocks of 96 trials (total of 25 minutes) were presented varying by flanker type: - Congruent - Incongruent - Neutral - Single and reinforcement condition: - No Reward or Response Cost	NA	Influence of extrinsic motivation on response time (RT) and accuracy as measures of interference control (ability to suppress competing distracters to carry out a target response)	Significant between-group differences on FSIQ (Wechsler Intelligence Scale for Children-4th Edition): AE < ADHD < CON Inhibitory control performance: - Accuracy: AE was significantly slower than ADHD ($p = 0.038$) and CON ($p < 0.001$) and	- Study was part of a larger project at Centre for Behavioural Teratology at San Diego State University. Flanker task was the third	Moderate (ROBINS-I)
	Alcohol-exposed (AE): - Inclusion: heavy	idiopathic ADHD (ADHD): - inclusion criteria: ADHD	Controls (CON): - exclusi							

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
	PAE - exclusion: other known causes of mental deficiency, adopted from abroad after age of 5, head injury involving loss of consciousness, physical or psychiatric conditions that prevented involvement - Analysed: n = 34 - Analysed with ADHD symptoms: n = 29	- exclusion: greater than minimal PAE (average exposure < 1 drink per week and no more than 2 drinks per occasion) - Analysed: n = 23	on: indicators of ADHD; subclinical symptoms of ADHD on the C-DISC-4.0 - Analysed: n = 31		(NR) - Reward Only (REW) - Reward + Occasional Response Cost (ROR) - Equal Probability of Reward and Response Cost (EQ) Points were earned or lost based on speed and accuracy and were shown on screen (feedback and extrinsic motivation). Prize corresponding to the points at the end.			significantly slower in incongruent trials compared to congruent trials ($p < 0.001$) - RT: AE had significantly poorer accuracy in incongruent trials than CON ($p = 0.001$) and significantly poorer accuracy in incongruent trials compared to congruent trials ($p < 0.001$). Age significantly interacted with condition [$F(1.235, 103.725) = 7.74$, $p = 0.004$, $\eta p2 = 0.084$] and flanker type [$F(2.144, 180.130) = 4.24$, $p = 0.014$, $\eta p2 = 0.048$]. Response to rewards: - In all conditions, AE was significantly slower than CON ($p < 0.001$) and slower than ADHD ($p = 0.046$; except for REW, $p = 0.051$) - For all groups, RT in the NR condition was significantly slower than in the other conditions ($p = 0.002$) - For AE ($p > 0.39$) and ADHD ($p > 0.19$), RT was similar	out of four computerized attention tasks that lasted about 1 h and 45 minutes in total and required a long duration of attention (possible impact on outcome) - Children were asked to abstain from medication use the day of testing. However, 7 AE and 2 ADHD took medication - AE showed greater difficulties with executive control - Regarding RT, AE and ADHD benefited similarly from both types of	

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention	Control	Outcomes	Results	Comments	Risk of Bias
								for all 3 reinforcement conditions - For CON, ROR improved RT compared to REW ($p = 0.03$) - All groups improved with reinforcement in RT, but CON showed the most improvement in RT when response cost was applied. For AE and ADHD, type of reinforcement was not critical. - For RT, main effect of group [$F(1, 84) = 10.69$, $p < 0.001$, $\eta p2 = 0.203$] with AE being slower than CON and ADHD $p < 0.017$) - For RT, main effect of flanker type [$F(2.144, 180.130) = 11.70$, $p < 0.001$, $\eta p2 = 0.122$]. RTs were significantly slower without reinforcement ($p < 0.001$) - For congruent trials, accuracy was better in the NR condition compared to REW ($p = 0.03$) and ROR ($p = 0.01$) - For incongruent	extrinsic reinforcement - Regarding accuracy, all groups showed better performance without reinforcement for all conditions except for single targets - Study utilized primary and secondary reinforcement - Oppositional defiant disorder and conduct disorder have not been assessed - No child with ADHD symptoms had the hyperactive/impulsive type; all of them had the inattentive or combined	

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
							trials ($p < 0.001$) and neutral trials ($p < 0.029$), accuracy was better in the NR condition compared to all other conditions - Accuracy was poorer for incongruent trials compared to all other trials ($p < 0.001$) - For ROR, accuracy was significantly poorer for neutral trials compared to congruent trials ($p = 0.019$) - For EQ, accuracy was poorer for neutral trials compared to congruent ($p = 0.005$) or single trials ($p = 0.03$) - For accuracy, main effect of flaker type [$F(1.530, 130.049) = 118.06$, $p < 0.001$, $\eta p2 = .581$] and condition [$F(2.309, 196.230) = 37.01$, $p < 0.001$, $\eta p2 = 0.303$] - For accuracy, no main effect of group	type - Analyses were repeated without the 5 AE without ADHD => same results - IQ was significantly correlated with accuracy in AE and CON, and with RT in ADHD	
Kable et al. (2012) (28)	- Recruited from a multidisciplinary FAS diagnostic clinic - Inclusion for children: clinical diagnosis of FAS or pFAS (IOM Criteria) or significant	n = 23	Workshop group: - 2 days work	Internet group: - Web-based works	Standard Information group: - Paper form - Informatio	- Satisfaction - Knowledge about FASD - Behavioura	Satisfaction (Likert scale response and open-ended questions):	- Gender differences between the groups	Moderate (ROB-2)

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
RCT	levels of alcohol-related dysmorphology (standard pediatric dysmorphia checklist) - Inclusion for adults: parents or caregivers of children - Mean age of participating children: 6–7 years				shop in-person (each 2h) - Education about FASD, information on effective behaviour management strategies, and advocacy tools	hops - Education about FASD, information on effective behaviour management strategies, and advocacy tools	n packets regarding the diagnosis, neurodevelopmental consequences and access to community services and information sources	l changes in children	- All groups: high satisfaction - Workshop group: higher ratings on usefulness, understandability, amount, overall satisfaction, and willingness to recommend than Standard Information group - Workshop group: higher ratings on amount of information and overall satisfaction than Internet group Knowledge (Caregiver advocacy knowledge questionnaire (CA) and Behavioural regulation knowledge questionnaire (BR)): - Standard Information group: significant gains in knowledge on behavioural regulation (BR: $t(17) = -2.7$, $p < 0.01$, $\eta p^2 = 0.305$); only trend for improvement on the caregiver advocacy knowledge (CA: $t(17) = -1.9$, $p < 0.08$, $\eta p^2 = 0.170$) - Workshop group: significant gains in both areas of knowledge:	as a potential reason for the Internet group not showing sign. Improvements - Significantly more participants with a higher dysmorphia score dropped out of the Internet group. This trend was also seen in the Standard Information group, but not in the Workshop group. - Initiation of the Internet group was the biggest hurdle (once logged in the method was effective). - Caregiver educational level had the strongest relationship with knowledge gains in the	
	Workshop group: - Recruited: n = 29 - Analysed: n = 23	Standard Information group: - Recruited: n = 24 - Analysed: n = 18	Internet group: - Recruited: n = 29 - Analysed: n = 18								

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
									Caregiver advocacy (CA: t (21) = −3.9, p < 0.001, ηp^2 = 0.422; BR: (t (11)= −6.7, p < 0.0001, ηp^2 = 0.668) - Internet group: significant gains in both areas of knowledge (CA: t (11) = −2.8, p < 0.02, ηp^2 = 0.412; BR: (t (11) = −3,4, p < 0.005, ηp^2 = 0.526) - Significant time effect and group effect - No significant group*time effect, but a trend was found on the BR data (F (2, 50) = 2.0, p < 0.152, ηp^2 = 0.073) for the Internet group gaining more knowledge than the Standard Information group. - Strongest relationship between caregiver educational level and knowledge gains was in the Standard Information group (CA: r = − 0.36, p < 0.16 and BR: r = 0.44, p < 0.08) as compared to the Workshop (CA: r = −0.15, p < 0.52 and BR: r = 0.25, p < 0.26) and Internet (CA: r = −0.03, p < 0.93 and BR: r = 0.18, p <	Standard Information group (not significant). - Only 50 % of the children showed improvements, only 25 % showed significant improvements => only effective for some families - Content differences between Standard Information group and Workshop group/Internet group	

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
									0.57) groups. Child behavioural changes (Children behaviour checklist): - Standard Information group: trend in improving total problem behaviour (t (1, 17) = 1.8, $p < 0.09$, $\eta p^2 = 0.164$) and externalizing problem behaviour (t (1, 17) = 2.0, $p < 0.06$, $\eta p^2 = 0.192$) - Workshop group: For total problem behaviours, a significant effect was found (t (1, 21) = 2.7, $p < 0.014$, $\eta p^2 = 0.254$) - Internet group: no changes in total problem behaviour - On the total problems scale, a significant treatment by group effect was found (F (2, 50) = 3.2, $p < 0.048$, $\eta p^2 = 0.115$) with improvements in behavioural ratings only in the Standard Information and Workshop groups. - On the externalizing scale, a significant general treatment effect by gender (F (1, 50) = 5.3, $p < 0.026$, $\eta p^2 =$		

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
									0.096) was found with males showing greater improvements than females and a trend was found for a time by group effect ($F(2, 50) = 2.9$, $p < 0.064$, $\eta p^2 = 0.104$) with those in the Standard Information and Workshop groups showing improved behaviour but those in the Internet group not. For the internalizing scale, there was a trend for a general treatment effect ($F(1, 50) = 2.2$, $p < 0.14$, $\eta p^2 = 0.043$) with post-test scores being lower than those at pre-test. - Examination of the pattern of change scores found on the externalizing and total problem scores suggested that the treatment effects were skewed (Externalizing = 1.175 and Total = 1.492) such that about 50 % of participants made positive gains with half of these making what could be termed clinically		

Reference Study Type	Participants (Number and Characteristics)			Drop-outs	Intervention		Control	Outcomes	Results	Comments	Risk of Bias
									significant changes (> 1/2 of standard deviation).		

RCT – randomized controlled trials, ROBINS-I – Tool for assessing risk of bias in non-randomised studies of interventions, ROB-2 – Cochrane risk-of-bias tool – 2nd Version

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Risk of bias assessment – systematic reviews

Reference	Last search	Country	Included articles (N)	Types of included articles	Programs or Intervention types	Population (age in years)	Population (characteristics)	Outcomes reported	Results	Comments	Critical appraisal modified after AMSTAR-2
Flannigan et al. (2020) (1)	01.04.2020	Canada	33	Inclusion: original and peer-reviewed, contributed empirical data (quantitative, qualitative, or mixed), and included the following: (i) interventions for individuals of any age with PAE or FASD, (ii) with quantitatively or qualitatively reported outcomes related to mental health and/or substance use, and (iii) published in English, from the year 2000 onward. Exclusion: animal studies; dietary or pharmalogical interventions	Any intervention to improve mental health (emotional, psychological, spiritual, behavioural, and social well-being) and substance use outcomes	All age groups	Any individuals with PAE and FASD	Mental health (emotional, psychological, spiritual, behavioural, and social well-being) and substance use outcomes	- Supporting Attachment and Family Wellness: All interventions included caregiver components; Interventions were original and specifically designed for the PAE/FASD child–caregiver dyad and may be particularly (although not necessarily exclusively) impactful in early childhood. They had positive impacts on attachment and child adjustment, including improved relationships, enhanced caregiving experiences, and increased family functioning. They support a preventative model in which better bonding may aid the developmental process in the child and diminish the risk of adversity. - Building Skills and Strategies (Self-regulation, Behavioural Skills, Social Skills, Mental Health Literacy): Nearly half of the interventions involved caregiver/teacher training. They were often conducted in middle childhood. Self-regulation and social skills strategies have the strongest evidence for use in children with PAE/FASD, and there is promising evidence for interventions to support the development of positive behavioural skills and strategies. Skill-building was not exclusive to the individual with PAE/FASD; in many cases, interventions also incorporated external support	Most studies were RCTs (n = 12) and controlled clinical trials (CCTs; n = 8); 4 were case studies, 3 were case series, 3 were cohort (before and after) studies, one was a file review, one was an implementation study, and one was an exploratory study.	1. PICO: Yes (no comparator needed) 2. Protocol: Yes 3. Study selection: No 4. Search strategy: Yes 5. Selection in duplicate: Yes 6. Extraction in duplicate: Yes 7. Excluded studies: No 8. Included studies: Partial Yes 9. RoB: Yes; Yes 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in dicussion: Yes 14. Heterogeneity: Yes 15. Publication bias: NA 16. Conflicts: Yes Low RoB

									through facilitators, caregivers, teachers, or mentors. Importantly, these interventions led to improved indicators of mental health, suggesting that the acquisition of skills and strategies is one viable mechanism for individuals with FASD (and their families), to cope, interact, and feel better. - Responding to Risk and Reducing Harm (Substance Use, Justice Involvement): In later adolescence and adulthood, as needs may become more complex, interventions shifted to a more responsive approach to mitigate risk and reduce harm. => Importance of caregivers and their active and intensive participation => Combined, these approaches may reflect the components critical to integrated and interdependent care planning for individuals with PAE/FASD across the life course.		
Mela et al. (2018) (2)	04.02.2017	Canada	25	Only peer-reviewed journal articles will be sourced or identified. No gray literature searches. Articles will be restricted to English or transcribed English, no timeline restrictions, only human studies to be included, no restrictions to study design	All literature evaluating pharmacological interventions for children and adults living with FASD	All age groups	Adults and children either diagnosed with FASD or who are at risk of having FASD	benefits and risks of psychotropic medications on patients (adults and children) diagnosed with FASD	- Hyperactivity and inattention: Inattention was found to respond better to Dextroamphetamine than Methylphenidate, but a high adverse event profile induced discontinuation. Atomoxitine may be useful in the inattention domain of FASD due to its noradrenergic stimulation effect. - Social skills: Stimulants were found to be less efficacious compared to second-generation neuroleptics, specifically in the domain of social skills. Stimulants showed comparatively poor response both as monotherapy and in combination with	Very poor studies included: animal studies, not only patients with FASD, study with 4 participants, placebo group with 1 child, no medication at all => critical! A standardized critical appraisal of the studies was done, but the risk of bias or level of evidence is not recorded for the studies included Not all included studies are reported in the discussion No real results/conclu	1. PICO: Yes (no comparator needed) 2. Protocol: Yes 3. Study selection: No 4. Search strategy: Yes 5. Selection in duplicate: Yes 6. Extraction in duplicate: Yes 7. Excluded studies: No 8. Included studies: Partial No 9. RoB: Yes; No information (RoB is

									neuroleptics. Greater improvement was found with neuroleptics compared to those not prescribed neuroleptics (with and without combination with stimulants) - Seizure disorders: Second-generation antipsychotics are used to treat complications of seizure disorders, as adjunct therapy for Conduct Disorder, for disruptive behaviour in children with low IQ, and for secondary disabilities associated with FASD. - Short-term aggressiveness: Risperidone has demonstrated strong benefits in the treatment of short-term aggressiveness in some research => but too low evidence - Appetite: Risperidone has the tendency to increase appetite - Adverse effects: There is concern for long-term use of Risperidone because of the metabolic risk associated with most second-generation antipsychotics as well as having the potential for extrapyramidal symptoms and altering the dopaminergic system. - Depression: Antidepressants such as SSRI, SNRIs, NRIs, and TCAs are a class of medication prescribed for those diagnosed with FASD in the context of depression. - ADHD symptoms: SSRIs were reported as effective in treating ADHD symptoms when those coexist with behaviour problems such as outbursts, aggression, and compulsive behaviours in children with FASD. Atomoxetine	sion	not documented!!) 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in discussion: No 14. Heterogeneity: No 15. Publication bias: NA 16. Conflicts: Yes Critical RoB because of the studies included

									appears to be less effective than Methylphenidate in children with an IQ below 85. ADHD symptoms can be treated with a stimulant such as Adderall or Dexedrine. - In paediatric patients living with FASD, a lot of medications used are "off label". - The choice of medication should be based on the most relevant diagnosis causing functional impairment or targeting two co-existing diagnoses.		
Reid et al. (2015) (3)	NI	Australia	32	No restrictions on the types of study designs Inclusion: Non-pharmacologial intervention studies that aim to improve an aspect of functioning Exclusion: Studies that evaluate diagnostic services	non-pharmalogical interventions	all age groups	Any individuals with FASD	Improvements in functioning for people with a FASD e.g. adaptive, cognitive, self-regulation, social skills, behaviour	- Developmental outcomes in infants: Mixed results: 1 study showed that following their intensive home visiting service, children with PAE scored in the average range on developmental tests. 1 study with a considerably stronger design found no effect of the home visiting service on the same measures of developmental outcome, with children scoring significantly below age-expected norms. - Self-regulation and attentional control (early to middle childhood): ALERT showed to be effective in improving executive functioning and showed changes in grey matter volume in critical regions for self-regulations. A computerised progressive attention program (CPAP) showed significant decrease in reaction times and distractibility, and significant improvement in auditory sustained attention. Activities from the pay attention training protocol with additional visual search tasks showed significant improvements in nonverbal reasoning, auditory and visual sustained	No study had a strong quality for selection bias, or blinding. 19 had a strong study design (RCTs and controlled clinical trials) 27 used reliable and valid measures 17 had a strong for withdrawal/dropouts	1. PICO: Yes 2. Protocol: Yes 3. Study selection: No 4. Search strategy: partial yes 5. Selection in duplicate: Yes 6. Extraction in duplicate: No information 7. Excluded studies: No 8. Included studies: Yes 9. RoB: Yes 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in discussion: Yes 14. Heterogeneity: Yes 15. Publication bias: NA 16. Conflicts: Yes Low RoB

									attention and a trend for improved performance on alternating attention. A small study on cognitive control therapy (learning metacognitive skills) showed no gains in cognitive functioning. => Promising results, but limited follow-up - Specific skills: MILE showed to be effective in improving math knowledge, parent reported problem behaviour, improved nonverbal reasoning, reading comprehension, and mathematics reasoning. CPAP showed improvements in math and reading fluency. A virtual reality game of fire/street safety showed significantly better knowledge of fire/street safety immediately and at follow-up (1 week) and most children (72%) were able to generalize the information within a behavioural setting. Classroom-based literacy training showed improvements in specific language and literacy skills, but not in general scholastic skills. Experimental group rehearsal training showed increase in digit span scores. A cover, copy and compare spelling procedure showed an increase in number of words spelt correctly. A motor skill training (FAST) could not affect cortisol levels. - Social skills in 3-12 year olds: Child Friendship Training (CFT) showed improvements in social skills and a decrease in hostile attribution (maintained at follow-up). Children with PAE can be treated in community settings if interventions are suitable. A community-based social skills group		

									showed gains in parent-rated social skills. => Strong evidence for structured programs that include children and parents in helping to improve social skills. - Parenting skills: Families moving forward program showed improvement in parental self-efficacy, parent needs and parent self-care, and a reduction in child behaviour problems. A child interaction therapy and a parent-only parenting support and management program were both effective to reduce child behavioural problems and parent stress. A group workshop, an internet program and a standardized written information are effective to increase parental knowledge. The workshop and the written information are effective in improving child behaviour. => parents show improved well-being from support in managing their children's behaviour. - Support, education and advocacy: Coaching Families (CF) was effective in decreasing family's needs and caregiver stress and in increasing goals. Specialized FASD training for workers and foster caregivers showed significant decline in number of placement changes. Workshops for teachers showed improved classroom behaviour. Key worker and parent support program that provides support, education and liaison to existing intervention services showed a better understanding of FASD and increased emotional and practical support, but only a trend to improve caregiver		

									stress, parenting-self-confidence and child's behaviour.		
Ordenewitz et al. (2021) (4)	Sep 19	Germany	25	Intervention studies, randomized controlled trials (RCTs) for children and adolescents with FASD Language: English, German, French Date of publication: Since 01/01/2000	Any intervention	<18 years	Children and adolescents (<18 years), diagnosed with FASD (FAS, pFAS, ARND)	Effects on the affected CNS domain according to the German guideline for the diagnosis of FASD	Language/speech: Language and literacy training (LLT): FASD-children and healthy control group improved. FASD-Children in the LLT group did catch up to their peers in some subtests regarding their skills in written letters, reading, and spelling of words and nonwords. There was a statistically significant improvement with respect to phonological and literacy skills in the FASD- LLT group compared to the FASD-control group. Learning/memory skills: - Choline supplementation: no evidence for an effect on memory, executive function, and attention deficits. No effects of on neurocognitive development. But younger participants (<4 years) improved in behavioural imitation tasks more than older participants (4-5 years). Follow-up: statistically significant effect of choline on non-verbal visual-spatial reasoning and non-verbal working memory compared to the placebo group. - Verbal rehearsal: no statistically significant differences between the experimental and the control group regarding memory of numbers Executive functions: - ALERT with parents: ALERT-group displayed statistically significant improvements in executive functioning and emotional functioning	No quality analysis of included studies. But quality of studies is very high.	1. PICO: Yes 2. Protocol: No 3. Study selection: No 4. Search strategy: partial yes 5. Selection in duplicate: No 6. Extraction in duplicate: No information 7. Excluded studies: No 8. Included studies: Yes 9. RoB: No 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in discussion: Yes 14. Heterogeneity: Yes 15. Publication bias: NA 16. Conflicts: Yes Low RoB

									compared to the control group. - ALERT without parents: treatment effect on inhibition tasks in children and on parent-reported behavioural regulation. There was a positive treatment effects on emotional control and performance in an inhibition task after intervention. Arithmetic skills: - MILE with parents: increase in parents' knowledge of FASD, caregiver advocacy and behavioural regulation. Significantly less problematic behaviour in their children was reported after the study. MILE-group showed greater gains in math performance than those in the control group. Follow-up: further betterment in mathematical skills in the MILE-group compared to control. An extension of the program to 15 weeks did not lead to a more distinct treatment effect (math skills) compared to the 6-weeks-program. - MILE without parents: Evidence for the effectiveness of the MILE intervention without parent training. Attention: Sustained attention training: clear evidence for improvements in the intervention group compared to the controls in several domains of attention on direct child measures. But, both groups showed improvements in the teacher-rated domains in attention and executive functioning. Social skills and behaviour: - Workshop/ community/online: workshop- and community-groups		

									showed gains in overall behavioural functioning of their children. All groups improved knowledge of parents. - Step Up Intervention (SUI): A positive treatment effect for light/moderate drinkers in reducing alcohol consumption compared to controls was observed. For abstinent/infrequent drinkers, no changes in alcohol consumption were reported. - Families on Track (FoT) Program: Intervention increased caregivers' knowledge about FASD and their advocacy. Perceived needs of families decreased in both groups, with an observable trend for a larger decrease in the intervention group compared to the controls. A positive effect of FoT on parent-rated emotional regulation of the child was observable. - FAR strategy trough GoFAR game: Training of the FAR technique has benefits for the child. Parent training alone did not prove to be sufficient for behavioural changes of the child. Results indicated that parent engagement in the child's treatment is an integral part of behavioural improvements in children with FASD (less parent-reported disruptive behaviour of the children). GoFAR group showed greater improvements in behaviour than children in the FACELAND group. Positive treatment effects of the GoFAR program in attention and adaptive functioning. - Parent assisted		

									Children's Friendship Training (CFT): Results pointed towards enhancement in appropriate social skills (direct child measure) after the treatment that remained stable over a 3-month period. Parent-rated social skills and problematic behavioural patterns of their child enhanced notably after treatment. Decline in hostile attributions in peer group entry scenarios, which were maintained at a 3-months follow-up. Higher levels of self-regulation were associated with greater improvements in social skills after CFT. Treatment effects of the CFT program were further enhanced by neuroleptic medication, whereas stimulant medication or no medication at all did not ameliorate the outcomes. CFT-group benefitted from stronger increments in knowledge of appropriate social behaviours and in self-concept compared to children in the SOC group. Children with FASD demonstrated improvement in social skills and could be successfully integrated in social skills groups with children without PAE in a community mental health setting. No differences in parent reports of social skills between the CFT and SOC group occurred. However, there was an observable trend that some children in SOC became worse in parent-reported social skills, while children in CFT generally displayed advances after treatment.		

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ePub Document 3: Summary of Findings Tables (GRADE-Tables).

The quality of evidence for each outcome has been evaluated based on the GRADE criteria. However, due to variations in the composition of intervention and control groups, diverse test methodologies employed to assess intervention effects, differing methodological approaches, and inconsistent reporting across the included studies, a meaningful or standardized calculation of an effect estimator was not feasible. Consequently, no relative or anticipated absolute effects are presented in the subsequent tables.

Table 1: Summary of findings, drugs

Population†: children with FASD or high prenatal alcohol exposure **Setting**†: unknown **Intervention**†: methylphenidate, stimulants, neuroleptics **Comparison**†: diverse drugs, no comparison group, placebo										
Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		
Epilepsy (critical)	N = 10 (1x control study) [1]	1x very high	No	No	No	No	No	No	No	1 systematic review; only 1 study; very small sample	Very low ⨁⊖⊖⊖
Social skills and behaviour[a] (critical)	N† [1–3]	2x low,	No	Yes	No	No	No	No	No	2 systematic reviews; 13 studies; high data volume; only mild adverse effects	Moderate ⨁⨁⨁⊖

Attention[a] **(critical)**	N > 125 (1x RCT; 1x uncontrolled intervention study)† [1, 3]	1x low,	No	Yes	No	No	No	No	No	1 systematic review; teilweise very kleine Stichproben (N = 10); unterschiedliche Art an Medikamenten	Low ⨁ ⨁⊖ ⊖
Adverse effects[b] **(critical)**	N = 114 (uncontrolled intervention study) [3]	1x low	No	Yes	No	No	No	No	No	Nur 1 Studie; keine Placebo-Gruppe; kein Fokus auf Adverse effects	Moderate ⨁ ⨁ ⨁⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[b] Avoidance of adverse effects of the interventions

† Cannot be determined precisely due to the reporting of the systematic reviews

Literature:

1. Mela, M., Okpalauwaekwe, U., Anderson, T., Eng, J., Nomani, S., Ahmed, A., & Barr, A. M. (2018). The utility of psychotropic drugs on patients with Fetal Alcohol Spectrum Disorder (FASD): a systematic review. Psychiatry and Clinical Psychopharmacology, 28(4), 436-445. https://doi.org/10.1080/24750573.2018.1458429
2. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
3. Smiarowska, M., Brzuchalski, B., Grzywacz, E., Malinowski, D., Machoy-Mokrzynska, A., Pierzchlinska, A., & Bialecka, M. (2022). Influence of COMT (rs4680) and DRD2 (rs1076560, rs1800497) Gene Polymorphisms on Safety and Efficacy of Methylphenidate Treatment in Children with Fetal Alcohol Spectrum Disorders. Int J Environ Res Public Health, 19(8). https://doi.org/10.3390/ijerph19084479

Table 2: Summary of findings, supplements

Population: children with FASD
Setting: at home
Intervention: choline supplementation in different dosages
Comparison: placebo

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence -
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Kognitive Leistung / Intelligenz[a] (critical)	N = 91 (2x RCT) [1, 2]	2x low	No	No	No	No	Yes	No	No	Fishy body-odor as an adverse effect; only part of cognition; improvement only with latency; different test procedures; high lost-to-follow-up	High ⊕⊕⊕⊕
Executive functions[a] (critical)	N = 86 (2x RCT) [2, 3]	2x low	No	No	Yes	No	No	No	No	Only 2 studies, each with different age of children, duration and dose of medication; 1 follow-up; fishy body-odor as adverse effect	High ⊕⊕⊕⊕
Learning and memory[a] (critical)	N = 168 (4x RCT) [1–4]	4x low	No	Yes	Yes	No	No	No	No	No direct effect, not even in long-term memory; improvement only in non-verbal working memory and only with a latency of a few years; fishy body-odor as an adverse effect	Moderate ⊕⊕⊕⊖

Attention[a] **(critical)**	N = 86 (2x RCT) [2, 3]	2x low	No	Yes	No	No	Yes	No	No	High lost-to-follow-up; fishy body-odor as an adverse effect; positive effect only with latency	High ⊕ ⊕ ⊕ ⊕
Adverse effects[b] **(critical)**	N = 132 (3x RCT) [1, 3, 5]	3x low	No	Yes	No	No	No	Yes	No	Fishy body-odor as an adverse effect	High ⊕ ⊕ ⊕ ⊕

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[b] Avoidance of adverse effects of the interventions

Literature:

1. Wozniak, J. R., Fuglestad, A. J., Eckerle, J. K., Fink, B. A., Hoecker, H. L., Boys, C. J., Radke, J. P., Kroupina, M. G., Miller, N. C., Brearley, A. M., Zeisel, S. H., & Georgieff, M. K. (2015). Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr, 102(5), 1113-1125. https://doi.org/10.3945/ajcn.114.099168
2. Wozniak, J. R., Fink, B. A., Fuglestad, A. J., Eckerle, J. K., Boys, C. J., Sandness, K. E., Radke, J. P., Miller, N. C., Lindgren, C., Brearley, A. M., Zeisel, S. H., & Georgieff, M. K. (2020). Four-year follow-up of a randomized controlled trial of choline for neurodevelopment in fetal alcohol spectrum disorder. J Neurodev Disord, 12(1), 9. https://doi.org/10.1186/s11689-020-09312-7
3. Nguyen, T. T., Risbud, R. D., Mattson, S. N., Chambers, C. D., & Thomas, J. D. (2016). Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders. Am J Clin Nutr, 104(6), 1683-1692. https://doi.org/10.3945/ajcn.116.142075
4. Wozniak, J. R., Fuglestad, A. J., Eckerle, J. K., Kroupina, M. G., Miller, N. C., Boys, C. J., Brearley, A. M., Fink, B. A., Hoecker, H. L., Zeisel, S. H., & Georgieff, M. K. (2013). Choline supplementation in children with fetal alcohol spectrum disorders has high feasibility and tolerability. Nutr Res, 33(11), 897-904. https://doi.org/10.1016/j.nutres.2013.08.005
5. Smith, S. M., Virdee, M. S., Eckerle, J. K., Sandness, K. E., Georgieff, M. K., Boys, C. J., Zeisel, S. H., & Wozniak, J. R. (2021). Polymorphisms in SLC44A1 are associated with cognitive improvement in children diagnosed with fetal alcohol spectrum disorder: an exploratory study of oral choline supplementation. Am J Clin Nutr, 114(2), 617-627. https://doi.org/10.1093/ajcn/nqab081

Table 3: Summary of findings, transcranial direct current stimulation (tDCS)

Population: children with FASD

Setting: clinical setting

Intervention: transcranial direct current stimulation (tDCS)

Comparison: sham

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence -
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Executive functions[a] (critical)	N = 38 (RCT) [1]	1x low	No	No	No	No	No	No	No	Only 1 study; high effort; potential harm outweighs potential benefit	High ⊕⊕⊕⊕
Learning and memory[a] (critical)	N = 38 (RCT) [1]	1x low	No	No	No	No	No	No	No	Only 1 study; high effort; potential harm outweighs potential benefit	High ⊕⊕⊕⊕
Attention[a] (critical)	N = 38 (RCT) [1]	1x low	No	No	No	No	No	No	No	Only 1 study; high effort; potential harm outweighs potential benefit	High ⊕⊕⊕⊕
Adverse effects[b] (critical)	N = 38 (RCT) [1]	1x low	No	No	No	No	No	No	No	Only 1 study; high effort; potential harm outweighs potential benefit	High ⊕⊕⊕⊕

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[b] Avoidance of adverse effects of the interventions

Literature:

1. Boroda, E., Krueger, A. M., Bansal, P., Schumacher, M. J., Roy, A. V., Boys, C. J., Lim, K. O., & Wozniak, J. R. (2020). A randomized controlled trial of transcranial direct-current stimulation and cognitive training in children with fetal alcohol spectrum disorder. Brain Stimul, 13(4), 1059-1068. https://doi.org/10.1016/j.brs.2020.04.015

Table 4: Summary of findings, somatosensory trainings

Population: children with FASD

Setting: unknown

Intervention: The Neurosequential Model of Therapeutics (NMT) to determine the intervention elements from Parent-Child Psychotherapy (CPP) and Mindful Parenting Education (MPE)

Comparison: no comparison group

Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		
Development[a] (critical)	N = 10 (uncontrolled intervention study) [1]	1x high	No	Yes	Yes	No	Yes	No	no	Only 1 study; small sample; no follow-up; no differentiation between developmental subcategories	Very low ⨁⊖⊖⊖
Parental relief[f] (critical)	N = 10 (uncontrolled intervention study) [1]	1x high	No	Yes	Yes	No	Yes	No	no	Only 1 study; small sample; no follow-up	Very low ⨁⊖⊖⊖

Knowledge acquisition[g] (critical)	N = 10 (uncontrolled intervention study) [1]	1x high	No	Yes	Yes	No	Yes	No	no	Only 1 study; small sample; no follow-up	Very low ⨁⊖⊖⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[f] Relief for caregivers (biological, foster and adoptive parents, caregivers) and improving the quality of life of the entire family/institution affected family/institution

[g] Improving knowledge of the deviant state of health/disorder/disability and improvement of insight into the illness

Literature:

1. Zarnegar, Z., Hambrick, E. P., Perry, B. D., Azen, S. P., & Peterson, C. (2016). Clinical improvements in adopted children with fetal alcohol spectrum disorders through neurodevelopmentally informed clinical intervention: A pilot study. Clin Child Psychol Psychiatry, 21(4), 551-567. https://doi.org/10.1177/1359104516636438

Table 5: Summary of findings, balance trainings

Population: children with FASD

Setting: university, laboratory, at home

Intervention: The virtual reality system "Sensorimotor Training to Affect Balance, Engagement and Learning" (STABEL)

Comparison: inactive comparison group

Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		

Fine-/ graphomotor skills or gross motor coordination[a] (critical)	N = 45 (1x non-randomized control study; 1x uncontrolled study) [1, 2]	1x low,	No	Yes	Yes	No	No	No	No	Possible at home; little time required; uncertain clinical significance; worsening of postural stability and sensory attention (fatigue?); no follow-up	Low ⊕ ⊕⊖ ⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

Literature:

1. McCoy, S. W., Jirikowic, T., Price, R., Ciol, M. A., Hsu, L. Y., Dellon, B., & Kartin, D. (2015). Virtual Sensorimotor Balance Training for Children With Fetal Alcohol Spectrum Disorders: Feasibility Study. Phys Ther, 95(11), 1569-1581. https://doi.org/10.2522/ptj.20150124
2. Jirikowic, T., Westcott McCoy, S., Price, R., Ciol, M. A., Hsu, L. Y., & Kartin, D. (2016). Virtual Sensorimotor Training for Balance: Pilot Study Results for Children With Fetal Alcohol Spectrum Disorders. Pediatr Phys Ther, 28(4), 460-468. https://doi.org/10.1097/PEP.0000000000000300

Table 6: Summary of findings, language trainings

Population: children with FASD

Setting[†]: unknown

Intervention: language and literacy training

Comparison: inactive comparison group, children without FASD

Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade**					**Factors leading to quality upgrade**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		

Language[a] **(critical)**	N = 59 (control study) [1]	1x moderate	No	No	No	No	No	No	No	Systematic review with only 1 study; outcome is not receptive/expressive language	Moderate ⨁⨁⨁⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[†] Cannot be determined precisely due to the reporting of the systematic reviews

Literature:

1. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001

Table 7: Summary of findings, training for promoting mathematical thinking

Population: children with FASD **Setting**: school, at home, clinical setting **Intervention**: The Math Interactive Learning Experience (MILE) Program **Comparison**: The Social Skills Improvement System Intervention, inactive comparison group, parental education										
Outcomes (relevance)	**Number of participants (study design)**[4]	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations**[3]	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness**[2]	**Inconsistency**[2]	**Imprecision**[2]	**Publication bias**[2]	**Effect size**[2]	**Dose effect**[2]	**Residual plausible**		

Spatial-visual perception or spatial-constructive abilities[a] (critical)	N = 28 (control study) [1]	1x moderate	No	Yes	No	No	No	No	No	Only 1 study; no follow-up	Moderate ⨁⨁⨁⊖
Executive functions[a] (critical)	N = 28 (control study) [1]	1x moderate	No	Yes	No	No	No	No	No	Only 1 study, no follow-up; No clear advantage of an intervention	Moderate ⨁⨁⨁⊖
Mathematical skills[a]	N = 190[‡] (3x RCT, 1x control study) [1–4]	2x low,	Yes	No	No	No	Yes	No	No	2 systematic reviews; 4 studies; 2x same sample; comparison with skills training; 2x follow-up; with and without parental involvement; dependence on individual factors unclear	High ⨁⨁⨁⨁
Learning and memory[a] (critical)	N = 60 (RCT) [3]	1x moderate	No	Yes	Yes	No	No	No	No	Only 1 study; only parent assessment of the child's learning ability	Low ⨁⊖⊖
Attention[a] (critical)	N = 28 (control study) [1]	1x moderate	No	Yes	Yes	No	No	No	Yes	Only 1 study; no follow-up; no clear advantage of an intervention	Very low ⨁⊖⊖⊖
Learning and application of knowledge[d] (critical)	N = 60 (RCT) [3]	1x moderate	No	Yes	Yes	No	No	No	No	Only 1 study; only subjective assessment of learning behavior; transferability to everyday life unclear	Low ⨁⨁⊖⊖

Knowledge acquisition[g] (critical)	N = 60 (RCT) [3]	1x moderate	No	Yes	Yes	No	No	No	No	Only 1 study; intervention-specific effect unclear	Moderate ⊕⊕⊕⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[d] Suboutcome of: improving the participation of children/young people with FASD

[g] Improving knowledge of the deviant state of health/disorder/disability and improvement of insight into the illness

‡ Cannot be determined precisely due to overlaps in the study population

Literature:

1. Kully-Martens, K., Pei, J., Kable, J., Coles, C. D., Andrew, G., & Rasmussen, C. (2018). Mathematics intervention for children with fetal alcohol spectrum disorder: A replication and extension of the math interactive learning experience (MILE) program. Res Dev Disabil, 78, 55-65. https://doi.org/10.1016/j.ridd.2018.04.018
2. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
3. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2015). Community translation of the Math Interactive Learning Experience Program for children with FASD. Res Dev Disabil, 39, 1-11. https://doi.org/10.1016/j.ridd.2014.12.031
4. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903

Table 8: Summary of findings, Serious Games

Population: children with FASD
Setting: school
Intervention: the Caribbean Quest, Virtual Reality Game for fire safety, Virtual Reality Game for traffic safety
Comparison: no comparison group, comparison between two Serious Games

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence -
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Mathematical skills[a] (critical)	N = 17 (uncontrolled intervention study) [1]	1x moderate	No	Yes	Yes	No	No	No	No	Only 1 study; small sample; group consisted of children with FASD and ASD - no group difference calculated; only subjective improvement	Very low ⨁⊖⊖⊖
Learning and memory[a] (critical)	N = 17 (uncontrolled intervention study) [1]	1x moderate	No	Yes	No	No	No	No	No	Only 1 study; small sample; group consisted of children with FASD and ASD - no group difference calculated	Very low ⨁⊖⊖⊖
Danger to self/others[c] (critical)	N = 21 (2x control study) [1]	1x low	No	No	No	No	No	No	No	1 systematic review; very small sample	Low ⨁⨁⊖⊖
Learning and application of knowledge[d] (critical)	N = 17 (uncontrolled intervention study) [1]	1x moderate	No	Yes	No	No	No	No	No	Only 1 study; small sample; group consisted of children with FASD and ASD - no group difference calculated; only subjective, qualitative assessment of teachers	Very low ⨁⊖⊖⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2
[2] "Yes" if at least one publication fulfills this criterion
[3] Some of the comments relate only to single publications
[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD
[c] Suboutcome of: reduction of complications/secondary diseases
[d] Suboutcome of: improving the participation of children/young people with FASD

Literature:

1. Kerns, K. A., Macoun, S., MacSween, J., Pei, J., & Hutchison, M. (2017). Attention and working memory training: A feasibility study in children with neurodevelopmental disorders. Appl Neuropsychol Child, 6(2), 120-137. https://doi.org/10.1080/21622965.2015.1109513

Table 9: Summary of findings, neurocognitive trainings

Population: children with FASD **Setting**[†]: clinical setting, at home, university, community setting **Intervention**: (adapted) Alert-program with/without parental training, GoFAR, The Caribbean Quest; Computerised Progressive Attention Program (CPAP), training based on Pay Attention Training Protocol **Comparison**: inactive comparison group, waiting list, training for emotional recognition (FACELAND), no comparison group										
Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		

Executive functions[a] **(critical)**	N = 151 (1x RCT, 2x control study) [1–3]	2x moderate,	Yes	No	Yes	No	Yes	No	Yes	3 studies; applicability to everyday life unclear; 2 studies by the same working group; large sample	Moderate ⊕⊕⊕⊖
Attention[a] **(critical)**	N = 105 (2x RCT, 2x control study 1x uncontrolled intervention study) [4–8]	2x low,	Yes	Yes	Yes	No	Yes	No	No	2 systematic reviews; 5 studies; overlap with other therapies; influence of parents unclear	Moderate ⊕⊕⊕⊖
Quality of life[e] **(critical)**	N = 27 (RCT) [9]	1x moderate	Yes	Yes	No	No	No	No	No	Nur 1 Studie; nur allgemeine Beeinträchtigung ermittelt	Low ⊕⊕⊖⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[e] Improving the quality of life of children/adolescents with FASD

[†] Cannot be determined precisely due to the reporting of the systematic reviews

Literature:

1. Nash, K., Stevens, S., Greenbaum, R., Weiner, J., Koren, G., & Rovet, J. (2015). Improving executive functioning in children with fetal alcohol spectrum disorders. Child Neuropsychol, 21(2), 191-209. https://doi.org/10.1080/09297049.2014.889110
2. Soh, D. W., Skocic, J., Nash, K., Stevens, S., Turner, G. R., & Rovet, J. (2015). Self-regulation therapy increases frontal gray matter in children with fetal alcohol spectrum disorder: evaluation by voxel-based morphometry. Front Hum Neurosci, 9, 108. https://doi.org/10.3389/fnhum.2015.00108
3. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
4. Kerns, K. A., Macoun, S., MacSween, J., Pei, J., & Hutchison, M. (2017). Attention and working memory training: A feasibility study in children with neurodevelopmental disorders. Appl Neuropsychol Child, 6(2), 120-137. https://doi.org/10.1080/21622965.2015.1109513
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fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
6. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903
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8. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
9. Petrenko, C. L. M., Pandolfino, M. E., & Robinson, L. K. (2017). Findings from the Families on Track Intervention Pilot Trial for Children with Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 41(7), 1340-1351. https://doi.org/10.1111/acer.13408

Table 10: Summary of findings, emotion regulation trainings

Population: shildren with FASD, Children with high prenatal alcohol exposure

Setting: slinical setting, at home, university, community setting

Intervention: GoFAR, Alert, The Caribbean Quest, Families on Track

Comparison: inactive comparison group, waiting list, training for emotion recognition (FACELAND), no comparison group, feedback from caregivers

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence - GRADE
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Social skills and behaviour[a] (critical)	N = 259 (6x RCT, 1x control study, 1x uncontrolled intervention study)[‡] [1–8]	8x moderate	No	Yes	No	No	Yes	No	Yes	8 studies; large amount of data; follow-ups; long-term effect questionable; 3x same sample; 2x same sample; dependence on individual factors unclear	High ⊕⊕⊕⊕

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] „Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[‡] Cannot be determined precisely due to overlaps in the study population

Literature:

1. Kerns, K. A., Macoun, S., MacSween, J., Pei, J., & Hutchison, M. (2017). Attention and working memory training: A feasibility study in children with neurodevelopmental disorders. Appl Neuropsychol Child, 6(2), 120-137. https://doi.org/10.1080/21622965.2015.1109513
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3. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
4. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
5. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
6. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. C. (2015). A metacognitive strategy for reducing disruptive behavior in children with fetal alcohol spectrum disorders: GoFAR pilot. Alcohol Clin Exp Res, 39(11), 2224-2233. https://doi.org/10.1111/acer.12885
7. Petrenko, C. L. M., Pandolfino, M. E., & Robinson, L. K. (2017). Findings from the Families on Track Intervention Pilot Trial for Children with Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 41(7), 1340-1351. https://doi.org/10.1111/acer.13408
8. Petrenko, C. L. M., Demeusy, E. M., & Alto, M. E. (2019). Six-Month Follow-up of the Families on Track Intervention Pilot Trial for Children With Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 43(10), 2242-2254. https://doi.org/10.1111/acer.14180
9.

Table 11: Summary of findings, social skills trainings

Population: children with FASD **Setting**: clinical setting **Intervention**: Children's Friendship Training with/without neuroleptics **Comparison**: standard care											
Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		

Social skills and behaviour[a] (critical)	N = 567‡ (6x Control study) [1–4]	3x low,	No	Yes	Yes	No	Yes	No	Yes	2 systematic reviews; 6 studies; partly the same samples; good feasibility; low effort; large sample	Moderate ⨁⨁⨁⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

‡ Cannot be determined precisely due to overlaps in the study population

Literature:

1. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
2. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903
3. O'Connor, M. J., Laugeson, E. A., Mogil, C., Lowe, E., Welch-Torres, K., Keil, V., & Paley, B. (2012). Translation of an evidence-based social skills intervention for children with prenatal alcohol exposure in a community mental health setting. Alcohol Clin Exp Res, 36(1), 141-152. https://doi.org/10.1111/j.1530-0277.2011.01591.x
4. Regehr, E. (2015). The Impact of an Intervention on Social Skills of Young Children with Prenatal Alcohol Exposure [Master's Thesis, University of Alberta]. Alberta. https://dx.doi.org/10.7939/r3b56dc77

Table 12: Summary of findings, neurocognitive trainings combined with parental trainings

Population: children/adolescents with FASD and their caregivers **Setting**: university, clinical setting **Intervention**: Project Step-up, GoFAR, Alert, Children's Friendship Training, Families on Track **Comparison**: written information, FACELAND, inactive comparison group, standard care, feedback from caregivers					
Outcomes (relevance)	**Number of participa**	**Factors leading to quality downgrade:**	**Factors leading to quality upgrade:**	**Other factors to consider when making**	**Certainty**

	nts (study design)[4]	Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible	recommendations[3]	of the evidence - GRADE
Attention[a] (critical)	N = 60 (2x RCT) [1, 2]	2x moderate	No	Yes	Yes	No	Yes	No	No	Only 2 studies; 2x same study population; small group sizes; high parental satisfaction	Moderate ⊕⊕⊕⊖
Risky alcohol/drug consumption[c] (critical)	N = 54‡ (2x RCT) [3, 4]	1x low,	No	Yes	No	No	Yes	No	Yes	2x same study; follow-up; good feasibility; high satisfaction	High ⊕⊕⊕⊕
Interpersonal interaction and relationship[d] (critical)	N = 145 (1x RCT, 1x control study) [5, 6]	2x moderate	No	Yes	No	No	Yes	No	Yes	2 studies; large sample; long-term effects unclear; transferability unclear	Moderate ⊕⊕⊕⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[c] Suboutcome of: reduction of complications/secondary diseases

[d] Suboutcome of: improving the participation of children/young people with FASD

‡ Cannot be determined precisely due to overlaps in the study population

Literature:

1. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
2. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
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4. Flannigan, K., Coons-Harding, K. D., Anderson, T., Wolfson, L., Campbell, A., Mela, M., & Pei, J. (2020). A Systematic Review of Interventions to Improve Mental Health and Substance Use Outcomes for

Individuals with Prenatal Alcohol Exposure and Fetal Alcohol Spectrum Disorder. Alcohol Clin Exp Res, 44(12), 2401-2430. https://doi.org/10.1111/acer.14490
5. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
6. O'Connor, M. J., Laugeson, E. A., Mogil, C., Lowe, E., Welch-Torres, K., Keil, V., & Paley, B. (2012). Translation of an evidence-based social skills intervention for children with prenatal alcohol exposure in a community mental health setting. Alcohol Clin Exp Res, 36(1), 141-152. https://doi.org/10.1111/j.1530-0277.2011.01591.x

Table 13: Summary of findings, emotion regulation training combined with parental trainings

Population: children with FASD, Children with high prenatal alcohol exposure

Setting: clinical setting, at home, university, community setting

Intervention: GoFAR, Alert, Families on Track

Comparison: inactive comparison group, waiting list, emotion regulation training (FACELAND), feedback from caregivers

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence -
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Social skills and behaviour[a] (critical)	N = 217‡ (6x RCT) [1–6]	6x moderate	No	Yes	No	No	Yes	No	No	6 studies; large amount of data; follow-ups; long-term effect questionable; partly same samples; dependence on individual factors unclear	High ⊕⊕⊕⊕

Knowledge acquisition[g] (critical)	N = 51[‡] (2x RCT) [5, 6]	2x moderate	No	Yes	No	No	Yes	No	No	2x same sample; follow-up; long-term effects	Moderate ⊕⊕⊕⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[g] Improving knowledge of the deviant state of health/disorder/disability and improvement of insight into the illness

[‡] Cannot be determined precisely due to overlaps in the study population

Literature:

1. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
2. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
3. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
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6. Petrenko, C. L. M., Demeusy, E. M., & Alto, M. E. (2019). Six-Month Follow-up of the Families on Track Intervention Pilot Trial for Children With Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 43(10), 2242-2254. https://doi.org/10.1111/acer.14180

Table 14: Summary of findings, social skills trainings combined with parental trainings

Population: children with FASD and their caregivers
Setting: clinical setting
Intervention: Children's Friendship Training with/without neuroleptics
Comparison: standard care

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence -
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Social skills and behaviour[a] (critical)	N = ca. 567[‡] (6x control study) [1–4]	3x low,	No	Yes	Yes	No	Yes	No	Yes	2 systematic reviews; 6 studies; partly same samples; good feasibility; low effort; large sample	Moderate ⊕⊕⊕⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[‡] Cannot be determined precisely due to overlaps in the study population

Literature:

1. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
2. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903
3. O'Connor, M. J., Laugeson, E. A., Mogil, C., Lowe, E., Welch-Torres, K., Keil, V., & Paley, B. (2012). Translation of an evidence-based social skills intervention for children with prenatal alcohol exposure in a community mental health setting. Alcohol Clin Exp Res, 36(1), 141-152. https://doi.org/10.1111/j.1530-0277.2011.01591.x
4. Regehr, E. (2015). The Impact of an Intervention on Social Skills of Young Children with Prenatal Alcohol Exposure [Master's Thesis, University of Alberta]. Alberta. https://dx.doi.org/10.7939/r3b56dc77

Table 15: Summary of findings, psychoeducation of parents/caregivers

Population: children with FASD and their caregivers

Setting: at home, clinical setting

Intervention: written information, group workshops, online workshop, GoFAR

Comparison: comparison between different forms, FACELAND, inactive comparison group

Outcomes (relevance)	Number of participants (study design)[4]	Factors leading to quality downgrade:					Factors leading to quality upgrade:			Other factors to consider when making recommendations[3]	Certainty of the evidence -
		Risk of Bias[1]	Indirectness[2]	Inconsistency	Imprecision[2]	Publication bias[2]	Effect size[2]	Dose effect[2]	Residual plausible		
Social skills and behaviour[a] (critical)	N = 59 (RCT) [1]	Moderate	No	Yes	Yes	No	Yes	No	Yes	Only 1 study; good applicability; transferable to other countries; low effort, low costs	Moderate ⨁⨁⨁⊖
Domestic life[d] (critical)	N = 30 (RCT) [2]	1x moderate	No	Yes	No	No	No	No	No	Only 1 study; good applicability; transferable to other countries; low effort, low costs	Moderate ⨁⨁⨁⊖
Parental relief[f] (critical)	N = 231[‡] (2x RCT, 1x uncontrolled study) [3–5]	3x moderate	No	Yes	No	No	Yes	Yes	No	3 studies; 2x same sample; follow-up; long-term effects unclear; dependent on individual factors; large sample	Moderate ⨁⨁⨁⊖
Knowledge acquisition[g] (critical)	N = 59 (RCT) [1]	1x moderate	No	No	Yes	No	Yes	No	No	Only 1 study; good applicability; transferable to other countries; low effort, low costs	Moderate ⨁⨁⨁⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[d] Suboutcome of: improving the participation of children/young people with FASD

[f] Relief for caregivers (biological, foster and adoptive parents, caregivers) and improving the quality of life of the entire family/institution affected family/institution

[g] Improving knowledge of the deviant state of health/disorder/disability and improvement of insight into the illness

[‡] Cannot be determined precisely due to overlaps in the study population

Literature:

1. Kable, J. A., Coles, C. D., Strickland, D., & Taddeo, E. (2012). Comparing the Effectiveness of On-Line versus In-Person Caregiver Education and Training for Behavioral Regulation in Families of Children with FASD. Int J Ment Health Addict, 10(6), 791-803. https://doi.org/10.1007/s11469-012-9376-3
2. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
3. Petrenko, C. L. M., Pandolfino, M. E., & Robinson, L. K. (2017). Findings from the Families on Track Intervention Pilot Trial for Children with Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 41(7), 1340-1351. https://doi.org/10.1111/acer.13408
4. Petrenko, C. L. M., Demeusy, E. M., & Alto, M. E. (2019). Six-Month Follow-up of the Families on Track Intervention Pilot Trial for Children With Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 43(10), 2242-2254. https://doi.org/10.1111/acer.14180
5. Leenaars, L. S., Denys, K., Henneveld, D., & Rasmussen, C. (2012). The impact of fetal alcohol spectrum disorders on families: evaluation of a family intervention program. Community Ment Health J, 48(4), 431-435. https://doi.org/10.1007/s10597-011-9425-6

Table 16: Summary of findings, extrinsic reinforcements

Population: children with prenatal alcohol exposure **Setting**: clinical setting **Intervention**: extrinsic reinforcements **Comparison**: children with ADHD, typically developed children, tasks without extrinsic reinforcements											
Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		

Attention[a] (critical)	N = 88 (control study) [1]	1x moderate	Yes	Yes	No	No	No	No	No	Only 1 study; low effort; no costs; good applicability; no negative consequences to be expected; no inactive comparison group; transferability to everyday life unclear	Low ⊕ ⊕⊖ ⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

Literature:

1. Graham, D. M., Glass, L., & Mattson, S. N. (2016). The Influence of Extrinsic Reinforcement on Children with Heavy Prenatal Alcohol Exposure. Alcohol Clin Exp Res, 40(2), 348-358. https://doi.org/10.1111/acer.12959

Table 17: Summary of findings, trainings focusing on mental health

Population: children with FASD/ Autism spectrum disorders / Intellectual disability

Setting: school

Intervention: "The Brain Unit mental health literacy program" and "Dialectical behavior therapy skill-building"

Comparison: inactive comparison group

Outcomes (relevance)	**Number of participants (study design)[4]**	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations[3]**	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness[2]**	**Inconsistency**	**Imprecision[2]**	**Publication bias[2]**	**Effect size[2]**	**Dose effect[2]**	**Residual plausible**		

Coping[h] **(critical)**	N = 133 (RCT) [1]	1x low	Yes	No	No	No	No	No	No	1 systematic review, only 1 study; large sample; feasibility unclear	Moderate ⨁⨁⨁⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[h] Improvement in coping and self-efficacy

Literature:

1. Flannigan, K., Coons-Harding, K. D., Anderson, T., Wolfson, L., Campbell, A., Mela, M., & Pei, J. (2020). A Systematic Review of Interventions to Improve Mental Health and Substance Use Outcomes for Individuals with Prenatal Alcohol Exposure and Fetal Alcohol Spectrum Disorder. Alcohol Clin Exp Res, 44(12), 2401-2430. https://doi.org/10.1111/acer.14490

Table 18: Summary of findings, animal-assisted therapies

Population: children with FASD

Setting: clinical setting

Intervention: therapy program with therapy dogs

Comparison: standard care

Outcomes (relevance)	**Number of participants (study design)**[4]	**Factors leading to quality downgrade:**					**Factors leading to quality upgrade:**			**Other factors to consider when making recommendations**[3]	**Certainty of the evidence -**
		Risk of Bias[1]	**Indirectness**[2]	**Inconsistency**	**Imprecision**[2]	**Publication bias**[2]	**Effect size**[2]	**Dose effect**[2]	**Residual plausible**		
Social skills and behaviour[a] **(critical)**	N = 33 (1x RCT) [1]	1x moderate	No	Yes	No	No	Yes	No	No	Only 1 study	Moderate ⨁⨁⨁⊖

Quality of life[e] (critical)	N = 33 (1x RCT) [1]	1x moderate	Yes	Yes	No	No	No	No	No	Only 1 study; only severity of disease determined	Low ⊕ ⊕⊖ ⊖

[1] Assessment: randomized controlled trials: ROB 2; non-randomized controlled trials: ROBINS-I; uncontrolled trials: adapted form of ROBINS-I; systematic reviews: AMSTAR-2

[2] "Yes" if at least one publication fulfills this criterion

[3] Some of the comments relate only to single publications

[4] For systematic reviews, the number of participants and study designs of the relevant studies in the review are presented

[a] Suboutcome of: improvement in the neuropsychological functions of children/adolescents with FASD

[e] Improving the quality of life of children/adolescents with FASD

Literature:

1. Vidal, R., Vidal, L., Ristol, F., Domenec, E., Segu, M., Vico, C., Gomez-Barros, N., & Ramos-Quiroga, J. A. (2020). Dog-Assisted Therapy for Children and Adolescents With Fetal Alcohol Spectrum Disorders a Randomized Controlled Pilot Study. Front Psychol, 11, 1080. https://doi.org/10.3389/fpsyg.2020.01080

ePub Table 2: Inclusion criteria (based on PICOS scheme) and exclusion criteria for the systematic literature review.

Inclusion criteria / PICOS scheme	
Population	Children and adolescents with fetal alcohol spectrum disorders (aged 0–18 years)
Intervention	• Drug therapies o Stimulants o Neuroleptics o Food supplements o Drugs to regulate the sleep rhythm • Non-drug therapies o Psychoeducation of the child/adolescent o Psychoeducation of parents/guardians/caregivers o Functional, non-drug intervention for the child/adolescent: ▪ Occupational therapy ▪ Physiotherapy ▪ Speech therapy ▪ Psychotherapy ▪ Training in specific school skills (e.g. mathematics) • Combined medical/non-medical interventions • Other functional therapies
Comparator	• No intervention • Placebo • Contextual effect • Alternative intervention • Pre-post comparison
Outcome	• Improvement in the neuropsychological functions of children/adolescents with FASD e.g. (relevance 8) o Cognitive performance/intelligence o Development o Epilepsy o language o Fine-/graphomotoric skills or gross motor coordination o Spatial-visual perception or spatial-constructive abilities o Executive functions o Mathematical skills o Learning and memory skills o Attention o Social skills and behaviour • Avoidance of adverse effects of the interventions (relevance 9) • Reduction of complications/secondary diseases e.g. (relevance 8) o Somatic diseases

	○ Psychiatric illnesses incl. addictions ○ Risky behaviour (risky alcohol/drug consumption, danger to self/others, suicidal acts) ○ School failure and drop-out (or higher rate of school leaving qualifications and vocational training) ○ Delinquency ○ Maltreatment ○ Hospitalization or other inpatient stays • Improving the participation of children/young people with FASD (relevance 9) ○ Learning and application of knowledge ○ General tasks and requirements ○ Communication ○ Mobility ○ Self-care ○ Domestic life ○ Interpersonal interaction and relationships ○ Important areas of life ○ Community, social and civic life • Improving the quality of life of children/young people with FASD (relevance 9) • Relief for caregivers (biological, foster and adoptive parents, caregivers) and improving the quality of life of the entire family/institution affected (relevance 8) • Improving knowledge of the deviant state of health/disorder/disability and improvement of insight into the illness (relevance 8) • Improvement in coping and self-efficacy (relevance 8)
Study Type	Inclusion of randomized controlled studies, cohort studies, case-control studies, systematic reviews and meta-analyses
Language	English, German
Exclusion criteria	
A1	Other diseases
A2	Studies with animals or in vitro
A3	No intervention
A4	Study types: case reports, letters, editorials
A5	Unsystematic reviews
A6	Age of the study group predominantly > 18 years (more than 80 %)
A7	Published before 2012
A8	Number of participants < 10

ePub Table 3: Search strategies of the systematic literature search.

Date of search: 9th of August, 2022

Databases used: Pubmed, Ebsco, Epistemonikos, Cochrane Library

The search queries consisted of three main components:

1. **Target Population – Fetal Alcohol Spectrum Disorder (FASD) and Related Terms:**
    - The search captures various terms related to **FASD** and associated conditions, including:
        - Direct terms: *Fetal Alcohol Spectrum Disorder*, *FASD*, *Alcohol-Related Birth Defects (ARBD)*, *Alcohol-Related Neurodevelopmental Disorder (ARND)*.
        - Combinations of terms such as *Fetus*, *Embryopathy*, *Prenatal*, *Antenatal* with *Alcohol* or *Ethanol* and various disease-related terms (*Syndrome*, *Disorder*, *Deficit*, *Effect*, *Exposure*).
        - MeSH terms to ensure comprehensive coverage.
2. **Interventions – Therapies, Medications, and Complementary Measures:**
    - **Non-pharmacological interventions:**
        - Therapeutic approaches such as *Psychotherapy*, *Psychoeducation*, *Neurofeedback*, *Biofeedback*, *Physiotherapy*, *Occupational Therapy*, *Sports Therapy*, *Exercise*, *Motor Activity*, *Relaxation Therapy*, *Workshops*, *Support Programs*, and *Education*.
    - **Pharmacological interventions:**
        - Medications and active substances, including *Psychostimulants*, *Psychotropic Drugs*, *Antipsychotics*, *SSRIs*, *SNRIs*, *Mood Stabilizers*, *Valproic Acid*, *Melatonin*, and other specific substances (e.g., *Methylphenidate*, *Atomoxetine*, *Benzodiazepines*).
    - **Nutritional approaches:**
        - *Dietary Supplements*, *Probiotics*, *Vitamins*, *Minerals*, and *Medicinal Plants*.
3. **Exclusion Criteria – Animal Studies and In-vitro Research (not always technically applicable):**
    - Studies involving *animals* or *in-vitro models* are excluded (terms such as *animal study*, *mice*, *rats*, *zebrafish*, etc.).

Filters and Restrictions (not always technically applicable):

- **Study Population:** Only humans (Filter: *Humans*).
- **Language:** Only English and German studies.
- **Timeframe:** Publications since 2012.

Database (date of search)	Query
Pubmed **(August, 9, 2022)**	((fetal alcohol spectrum disorder*[tw] OR (FASD*[tiab] AND alcohol*[tiab]) OR alcoholic related birth defect*[tiab] OR alcoholic related neurodevelopmental disorder*[tiab] OR (("fetus"[MH] OR fetus[tiab] OR foetus[tiab] OR fetal[tiab] OR foetal[tiab] OR embryopathy[tiab] OR prenatal*[tiab] OR antenatal*[tiab]) AND (alcohol*[tiab] OR ethanol[tiab]) AND (disease*[tiab] OR disorder*[tiab] OR syndrome*[tiab] OR deficit*[tiab] OR effect*[tiab] OR expos*[tiab]))) AND ((“therapeutics”[MH] OR “therapeutic use”[SH] OR “therapy”[SH] OR therap*[tiab] OR intervention*[tiab] OR treatment*[tiab] OR training*[tiab] OR stimulat*[tiab] ORprogram*[tiab] OR workshop*[tiab] OR support*[tiab] OR “education”[MH] OR education*[tiab] OR ergotherap*[tiab] OR physiotherap*[tiab] OR “Motor Activity”[MH] OR “Sports”[MH] OR sport*[tiab] OR exercise*[tiab] OR physical activit*[tiab] OR hippotherap*[tiab] OR horseback*[tiab] OR “Psychotherapy”[MH] OR psychotherap*[tiab] OR psychoeducation*[tiab] OR neurofeedback*[tiab] OR biofeedback*[tiab] OR rehabilitation*[tiab] OR “Relaxation”[MH] OR “Relaxation Therapy”[MH]) OR (“Chemicals and Drugs Category”[MH] OR Drug*[tiab] OR medication*[tiab] OR stimulant*[tiab] OR hormon*[tiab] OR “Pharmacological and Toxicological Phenomena”[MH] OR (drug*[tiab] AND (therap*[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR (medic*[tiab] AND (therap*[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR pharmaco*[tiab] OR psychotropic*[tiab] OR psychoactiv*[tiab] ORpsychiatric*[tiab] OR adrenergic*[tiab] OR antipsychotic*[tiab] OR analeptic*[tiab] OR psychostimulant*[tiab] OR (tranquilizing[tiab] AND (drug*[tiab] OR agent*[tiab] OR medicin*[tiab] OR medication*[tiab])) OR tryptamin*[tiab] OR melatonin*[tiab] OR methylphenidat*[tiab] OR amphetamin*[tiab] OR amfetamin*[tiab] OR dextroamphetamin*[tiab] OR dextroamfetamin*[tiab] OR dexedrin*[tiab] OR lisdexamphetamine Dimesylate*[tiab] OR lisdexamfetamine Dimesylate*[tiab] OR guanidin*[tiab] OR guanfacin*[tiab] OR atomoxetin*[tiab] OR bupropion*[tiab] OR neuroleptic*[tiab] OR risperidon*[tiab] OR pipamperon*[tiab] OR metylperon*[tiab] OR methylperon*[tiab] OR melperon*[tiab] OR benzodiazepin*[tiab] OR olanzapin*[tiab] OR aripiprazol*[tiab] OR quetiapine Fumarat*[tiab] OR seroquel*[tiab] OR chlorprothixen*[tiab] OR chlorprotixen*[tiab] OR methotrimeprazin*[tiab] OR levomepromazin*[tiab] OR promethazin*[tiab] ORprometazin*[tiab] OR chloral hydrat*[tiab] OR clonidin*[tiab] OR SSRI*[tiab] OR SNRI*[tiab] OR inhibitor*[tiab] OR fluoxetin*[tiab] OR citalopram*[tiab] OR cytalopram*[tiab] OR sertralin*[tiab] OR mood stabilizer*[tiab] OR valproic acid*[tiab] OR divalproex*[tiab] OR lamotrigin*[tiab] OR nutrition*[tiab] OR "Dietary Supplements"[MH] OR ((food*[tiab] OR diet*[tiab]) AND supplement*[tiab]) OR "plants, medicinal"[MH] OR probiotic*[tiab] OR vitamin*[tiab] OR mineral*[tiab]))) NOT (animal study[ti] OR animals study[ti] OR animal survey[ti] OR animals survey[ti] OR animal model*[ti] OR mice[MH] OR mice[ti] OR mouse[ti] OR rats[MH] OR rats[ti] OR rat[ti] OR zebrafish[ti] OR drosophila[ti] OR in vitro[ti]) Filter: Humans, English, German, since 2012
Ebsco **(August, 9, 2022)**	#1: SU (fetal alcohol syndrome* or fasd or fetal* alcohol spectrum disorder* or prenatal* alcohol exposure* or alcohol* related fetal damage* or alcohol* related birth defect* or alcohol* related neurodevelopmental disorder* or fetal alcohol exposure*) OR TI (fetal alcohol syndrome* or fasd or fetal* alcohol spectrum disorder* or prenatal* alcohol

	exposure* or alcohol* related fetal damage* or alcohol* related birth defect* or alcohol* related neurodevelopmental disorder* or fetal alcohol exposure*) OR AB (fetal alcohol syndrome* or fasd or fetal* alcohol spectrum disorder* or prenatal* alcohol exposure* or alcohol* related fetal damage* or alcohol* related birth defect* or alcohol* related neurodevelopmental disorder* or fetal alcohol exposure*) #2: SU (therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR motor Activit* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR Relaxation) OR TI (therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR motor Activit* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR Relaxation) #3: SU (Drug therapy OR Drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR Dietary Supplements OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*) OR TI (Drug therapy OR Drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR Dietary Supplements OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*) #4: SU (animal research* OR animal stud* OR animal survey OR animal model* OR mice OR mouse OR rat* OR zebrafish OR drosophila OR in vitro) OR TI (animal research* OR animal stud* OR animal survey OR animal model* OR mice OR mouse OR rat* OR zebrafish OR drosophila OR in vitro) #5: (#1 AND (#2 OR #3)) NOT #4

	Limited: since 2012
Epistemonikos **(August, 9, 2022)**	((title:((FASD AND alcohol*) OR "alcohol related birth defect" OR "alcohol related neurodevelopmental disorder" OR ((fetus OR foetus OR fetal* OR foetal* OR embryopathy OR prenatal* OR antenatal*) AND (alcohol* OR ethanol*) AND (disease* OR disorder* OR syndrome* OR deficit* OR effect* OR expos*))) OR abstract:((FASD AND alcohol*) OR "alcohol related birth defect" OR "alcohol related neurodevelopmental disorder" OR ((fetus OR foetus OR fetal* OR foetal* OR embryopathy OR prenatal* OR antenatal*) AND (alcohol* OR ethanol*) AND (disease* OR disorder* OR syndrome* OR deficit* OR effect* OR expos*)))) AND (title:(therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR relaxation) OR abstract:(therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR relaxation)) OR (title:(drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*) OR abstract:(drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*))) NOT (title:("animal study" OR "animals study" OR "animal survey" OR "animals survey" OR "animal model" OR "animal models" OR mice OR mouse OR rats OR rat OR zebrafish OR

	drosophila OR "in vitro")) Limited: since 2012 => 431 results Limited: systematic reviews => 168 results
Cochrane Library **(August, 9, 2022)**	[[Keywords: fetal* alcohol* syndrome*] OR [Keywords: fasd] OR [Keywords: fetal* alcohol* spectrum disorder*] OR [Keywords: prenatal* alcohol* exposure*] OR [Keywords: alcohol* related fetal* damage*] OR [Keywords: alcohol* related birth defect*] OR [Keywords: alcohol* related neurodevelopmental disorder*] OR [Keywords: fetal* alcohol* exposure*]] AND [[Keywords: therapeutic*] OR [Keywords: therap*] OR [Keywords: intervention*] OR [Keywords: treatment*] OR [Keywords: training*] OR [Keywords: stimulat*] OR [Keywords: program*] OR [Keywords: workshop*] OR [Keywords: support*] OR [Keywords: education*] OR [Keywords: ergotherap*] OR [Keywords: physiotherap*] OR [Keywords: motor activit*] OR [Keywords: sport*] OR [Keywords: exercise*] OR [Keywords: physical activit*] OR [Keywords: hippotherap*] OR [Keywords: horseback*] OR [Keywords: psychotherap*] OR [Keywords: psychoeducation*] OR [Keywords: neurofeedback*] OR [Keywords: biofeedback*] OR [Keywords: rehabilitation*] OR [Keywords: relaxation] OR [Keywords: drug therap*] OR [Keywords: drug*] OR [Keywords: medication*] OR [Keywords: stimulant*] OR [Keywords: hormon*] OR [[Keywords: drug*] AND [[Keywords: therap*] OR [Keywords: treatment*] OR [Keywords: intervention*]]] OR [[Keywords: medic*] AND [[Keywords: therap*] OR [Keywords: treatment*] OR [Keywords: intervention*]]] OR [Keywords: pharmaco*] OR [Keywords: psychotropic*] OR [Keywords: psychoactiv*] OR [Keywords: psychiatric*] OR [Keywords: adrenergic*] OR [Keywords: antipsychotic*] OR [Keywords: analeptic*] OR [Keywords: psychostimulant*] OR [[Keywords: tranquilizing] AND [[Keywords: drug*] OR [Keywords: agent*] OR [Keywords: medicin*] OR [Keywords: medication*]]] OR [Keywords: tryptamin*] OR [Keywords: melatonin*] OR [Keywords: methyl*enidat*] OR [Keywords: am*etamin*] OR [Keywords: dextroam*etamin*] OR [Keywords: dexedrin*] OR [Keywords: lisdexam*etamine dimesylate*] OR [Keywords: guanidin*] OR [Keywords: guanfacin*] OR [Keywords: atomoxetin*] OR [Keywords: bupropion*] OR [Keywords: neuroleptic*] OR [Keywords: risperidon*] OR [Keywords: pipamperon*] OR [Keywords: metylperon*] OR [Keywords: methylperon*] OR [Keywords: melperon*] OR [Keywords: benzodiazepin*] OR [Keywords: olanzapin*] OR [Keywords: aripiprazol*] OR [Keywords: quetiapine fumarat*] OR [Keywords: seroquel*] OR [Keywords: chlorprothixen*] OR [Keywords: chlorprotixen*] OR [Keywords: methotrimeprazin*] OR [Keywords: levomepromazin*] OR [Keywords: promethazin*] OR [Keywords: prometazin*] OR [Keywords: chloral hydrat*] OR [Keywords: clonidin*] OR [Keywords: ssri*] OR [Keywords: snri*] OR [Keywords: inhibitor*] OR [Keywords: fluoxetin*] OR [Keywords: citalopram*] OR [Keywords: cytalopram*] OR [Keywords: sertralin*] OR [Keywords: mood stabilizer*] OR [Keywords: valproic acid*] OR [Keywords: divalproex*] OR [Keywords: lamotrigin*] OR [Keywords: nutrition*] OR [Keywords: dietary supplement*] OR [[[Keywords: food*] OR [Keywords: diet*]] AND [Keywords: supplement*]] OR [Keywords: probiotic*] OR [Keywords: vitamin*] OR [Keywords: mineral*]] AND [Earliest: (01/01/2012 TO 08/31/2022)]

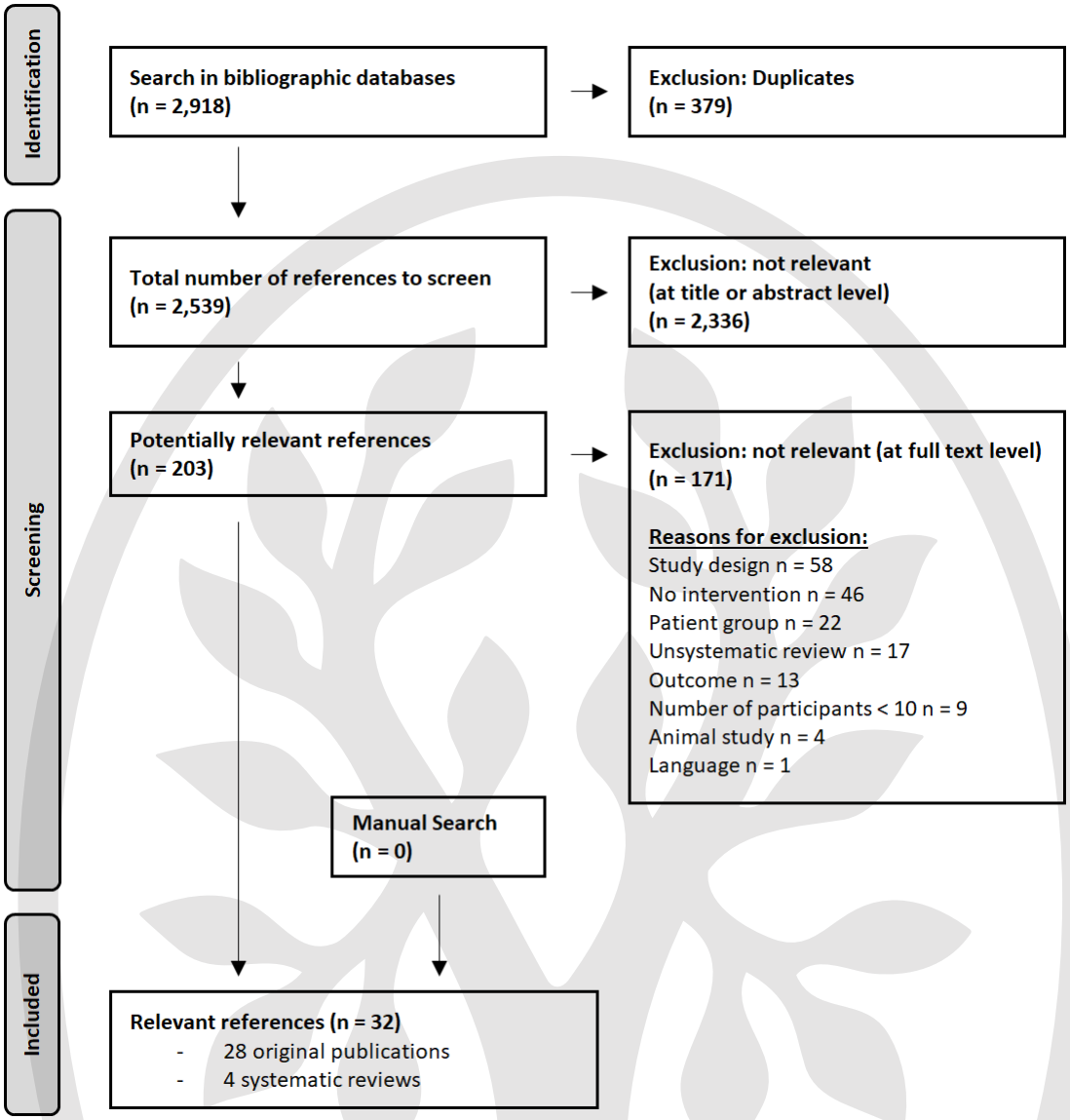

Figure 1: Flowchart of the systematic literature search.

First evidence-based guideline for interventions in FASD

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ABSTRACT

BACKGROUND

Prenatal alcohol exposure causes disruptions in brain development. The resulting disorder, fetal alcohol spectrum disorder (FASD), cannot be cured, but interventions can help improve the daily functioning of affected children and adolescents and the quality of life for the entire family.

OBJECTIVE

The aim of the German guideline version 2024 is to provide validated and evidence-based recommendations on interventions for children and adolescents with FASD.

METHODS

We searched for international guidelines and performed a systematic literature review and a hand search to identify literature (published 2012–2022) on interventions for children (0–18 years) with FASD. The quality of the literature was assessed for predefined outcomes using the GRADE method (Grading of Recommendations, Assessment, Development and Evaluation). We established a multidisciplinary guideline group, consisting of 15 professional societies, a patient support group and 10 additional experts in the field. The group agreed on recommendations for interventions based on the systematic review of the literature and

formulated additional recommendations, based on clinical experience/expert evidence in a formal consensus process.

RESULTS

No international guideline focusing on interventions for patients with FASD was found. 32 publications (4 systematic reviews, 28 original articles) were evaluated. The analysis resulted in 21 evidence-based recommendations and 26 expert consensus, covering the following topics: neuropsychological functioning, adverse effects of therapy, complications/secondary conditions, quality of life, caregiver burden, knowledge of FASD, and coping and self-efficacy.

CONCLUSION

The German guideline is the first internationally to provide evidence-based recommendations for interventions in children and adolescents with FASD.

1 INTRODUCTION

Fetal alcohol spectrum disorder (FASD) includes a range of conditions resulting from prenatal alcohol exposure (PAE) during pregnancy. Maternal alcohol consumption during pregnancy carries the risk of affecting fetal development, leading to lifelong physical, behavioral, and cognitive impairments. FASD serves as an umbrella term for three primary clinical entities: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and alcohol-related neurodevelopmental disorder (ARND), each manifesting with varying severity levels. However, there is ongoing debate regarding the classification of FASD

subtypes, with some definitions also including alcohol-related birth defects (ARBD) and neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE) as described in the DSM-5 [1].

With an estimated incidence of approximately 1.77%[2] of live births in Germany, FASD stands as one of the most prevalent chronic condition present at birth.

International guidelines have predominantly focused on evidence-based diagnostic criteria to facilitate early and precise identification of the disorder[3-6], laying the groundwork for ongoing care and support for children and adolescents with FASD and their families.

Tailored interventions (= measures designed to support the child's development and well-being) and support services addressing the specific needs of children and adolescents with FASD can mitigate the occurrence of secondary conditions and comorbidities of this disease, thus enhancing the quality of life for affected individuals and their social environment.

However, international guidelines seldomly provide specific recommendations for the care of individuals with FASD. Beyond diagnosis, guidelines primarily offer general advice for managing individuals with FASD, such as employing clear and simple language, maintaining routines, and structuring daily activities[7]. Various guidelines advocate for the use of management plans[7-9] and connecting individuals with FASD and their families to resources that may improve outcomes[7-13]. Emphasis is also placed on the importance of educating both patients and their entire social environment about the condition[7, 11, 12]. Policy-level guidelines focus on establishing basic infrastructures for improved care of individuals with FASD[14]. While some specific suggestions on interventions are based on expert and patient opinions or findings from focus groups[9, 11-13], these studies provide valuable insights into the lived experiences and practical needs of individuals with FASD and their caregivers. Despite these efforts, there remains a critical gap in evidence-based intervention recommendations

aimed at enhancing specific functions in individuals with FASD. The combination of qualitative findings and evidence-based research is essential for developing comprehensive, patient-centered care approaches. Therefore, addressing the gap in evidence-based recommendations is essential to improving outcomes for this population.

The German guideline presented here marks a significant advancement as the first internationally to provide evidence-based recommendations for interventions in children and adolescents with FASD. This represents a fundamental step towards improving the health and well-being of children with FASD.

2 METHODS

We tried to reduce potential bias in the guideline by ensuring a balanced composition of the guideline group, which was established in 2022 and consisted of representatives from 15 German professional societies, 10 FASD experts, and two members of the patient support group "FASD Deutschland". Additionally, two non-voting observers from the German Ministry of Health (Manuela Schumann, Kirsten Reinhard MD) participated in the guideline conferences and the consensus process was overseen by methodological supervisors and moderators (see ePub Table 1).

Each member of the consensus group provided a declaration of interest according to international requirements[15], which was reviewed by an independent person (conflict of interest officer). These declarations were discussed at the inaugural guideline conference

(1st July 2022). None of the consensus group members had conflicts of interest that warranted exclusion from the voting process or any related activities.

The project on which this publication is based was funded by the Innovation Fund of the Federal Joint Committee (Gemeinsamer Bundesausschuss – G-BA, funding code 01VSF21012). The funding did not influence the development and content of the guideline in any way.

The key question for the systematic literature search was consented in the first consensus conference and structured in PICOS format (PICOS: Population, Intervention, Comparator, Outcome, and Study design). The relevance of each outcome was rated on a 1 to 9 scale (1 to 3 – of limited importance; 4 to 6 – important but not critical; 7 to 9 – critical). The PICOS scheme, upon which the inclusion criteria for the systematic literature review were based, is detailed in ePub Table 2.

The key question was:

Which interventions (I) are associated with positive outcome criteria (O) compared to no interventions, placebos, contextual effects, alternative interventions, or a pre-post comparisons (C) in children and adolescents (0 to 18 years) with FASD (P)?

The “positive outcome criteria” were further specified into the following domains:

- Improvement in the neuropsychological functions of children/adolescents with FASD
- Avoidance of adverse effects of the interventions
- Reduction of complications/secondary diseases

- Improving the participation of children/young people with FASD
- Improving the quality of life of children/young people with FASD
- Relief for caregivers (biological, foster and adoptive parents, other caregivers) and improving the quality of life of the entire family/institution
- Enhancing knowledge of the health condition or disability and fostering insight into the associated challenges

The outcomes selected for this guideline address the multifaceted needs of children with FASD and their support systems. Improvement of neuropsychological functions was prioritized due to its alignment with the German S3 guideline on FASD diagnostics, reflecting its centrality to cognitive, emotional, and social development. Other outcomes, such as avoiding side effects, complications, and secondary conditions, highlight the importance of safe and preventive care. Enhancing participation, quality of life, and caregiver support aligns with person-centered approaches, acknowledging the critical role of families and social integration in successful interventions. Finally, knowledge dissemination and caregiver empowerment were included to address gaps in awareness and promote sustainable care practices. Together, these outcomes offer a comprehensive framework for improving both individual and systemic care for children and adolescents with FASD.

Based on our key question, we conducted a systematic literature search in the databases Medline via PubMed, Wiley Online Library via Cochrane Library, EBSCO (PsycINFO, PsycARTICLES, PSYNDEX), and Epistemonikos, covering English and German literature published between January 1, 2012, and August 9, 2022. EPub Tables 2 and 3 present the

search strategy and inclusion and exclusion criteria used to identify eligible publications, respectively.

The quality of evidence for outcomes was assessed using the GRADE method (Grading of Recommendations, Assessment, Development and Evaluation). Firstly, we evaluated the risk of bias of each publication individually using RoB 2 (Cochrane risk-of-bias tool – 2nd Version[16]) for randomized controlled trials, ROBINS-I („Tool for assessing risk of bias in non-randomized studies of interventions“[17]) for non-randomized controlled trials, a modified version of ROBINS-I instrument for non-controlled studies, and AMSTAR-2 instrument (A MeaSurement Tool to Assess systematic Reviews – 2nd Version[18]) for systematic reviews. Afterwards, we assessed the quality of evidence for each predefined outcome using the GRADE criteria (risk of bias/study limitations, indirectness, inconsistency of results, imprecision, publication bias, effect size, dose-response gradient, and the influence of residual and plausible confounders). The quality of evidence was categorized into four levels: very low, low, moderate, high.

Based on the evidence found in the literature, recommendations were formulated according to the requirements of the Association of the Scientific Medical Societies in Germany (AWMF): recommendations with the highest level A are expressed as “should”, followed by level B “ought to”, and the lowest level 0 “may be considered”.

In cases where insufficient evidence was available to make evidence-based recommendations, expert consensus was sought. This process involved gathering insights and opinions from professionals with extensive experience in the field. Experts were asked

to provide their perspectives on relevant interventions and practices, ensuring that recommendations were still grounded in practical expertise and current clinical experience. Expert consensus allowed us to address areas with limited or no empirical data, ensuring comprehensive guidance for practitioners despite the lack of robust evidence. These expert consensus were formulated accordingly to the evidence-based recommendations.

The recommendations and expert consensus for interventions in children and adolescents with FASD were discussed and modified by the guideline group in the third (31st March 2023), and fourth (7th June 2023) online consensus conference, considering evidence, clinical relevance, practical applicability, risk-benefit assessments and ethical considerations. Guided by an independent methodologically experienced moderators, the resulting recommendations and expert consensus were consented upon through a formal consensus process, utilizing the Nominal Group Technique [19]. For reaching "consensus" an agreement of > 75% of the participating guideline group members was required. "Strong consensus" represents an agreement of > 95%.

3 RESULTS

We identified a total of 2,539 publications after deduplication. We did not find any international guideline for interventions in children or adolescents with FASD. After title/abstract screening and full-text screening we included 32 publications (including four systematic reviews) for quality assessment (Figure 1). To access the complete list of publications included in the analyses, the risk of bias assessment, and the summary of findings tables (GRADE), please refer to ePub Documents 1, 2, and 3, respectively.

Figure 1: Flowchart of the systematic literature search.

The guideline group agreed on 21 evidence-based recommendations and 26 expert consensus. In the following, all recommendations and expert consensus are listed by outcomes. In compliance with AWMF regulations, the exact wording of the consented recommendations and expert consensus statements has been faithfully translated from German into English. This ensures that neither the content nor the phrasing is altered, maintaining the intended meaning and recommendation strength.

Expert consensus statements are marked with (EC).

For each recommendation, we provide the following information in parentheses:

1) Evidence grading (EG) based on the GRADE methodology, classified as:
    - low
    - moderate
    - high
2) Recommendation grading (RG), categorized as:
    - A = strong recommendation (“should”)
    - B = moderate recommendation (“ought to”)
    - 0 = open recommendation (“may be considered”)
3) The corresponding reference source

Additionally, background information is included where necessary.

Disclaimer: All interventions need to consider the individual circumstances of the person being treated as well as their social environment and their financial situation.

3.1 Improvement in the neuropsychological functions of children/adolescents with FASD

We divided this outcome into sub-outcomes according to the German guideline that identified specific functions of the central nervous system that are often impaired in individuals with FASD and, therefore, part of the diagnostic criteria[20, 21].

Table 1 shows the recommendations and expert consensus for the improvement of the neuropsychological functions, divided into ten FASD-relevant CNS domains.

Table 1: Recommendations for improving the neuropsychological functions of children/adolescents with FASD.

Sub-outcome	Recommendation/Expert consensus
Cognitive performance/ intelligence	• Children and adolescents with FASD and intellectual disability should not be excluded from guideline-based therapies (guideline "Intellectual disability")* (EC).
Development	• Infants, toddlers and primary school children with FASD should undergo developmental assessments at regular intervals so that developmental impairments can be diagnosed at an early stage and appropriate support measures can be initiated (EC).
Epilepsy	• In children with FASD and epilepsy, drug and non-drug therapies to reduce seizure symptoms should be based on the usual therapeutic measures and the guideline "Diagnostic principles for childhood epilepsy"* (EC).
Language	• For children with FASD, interventions to improve language development should be based on the guideline "Therapy of language development disorders"* (EC). • Regarding therapy, an interdisciplinary decision (including developmental diagnostics, speech pedagogy/logopedics, and psychology) ought to be made to ensure individually adapted support (EC).

Fine-/graphomotoric skills or gross motor coordination	• Interventions to improve coordination disorders in children with FASD should be based on the guideline "Circumscribed developmental disorders of motor functions"* (EC). • The support ought to be adapted to the child's neurological and neurocognitive impairments and, due to the common difficulty of transferring learned content, ought to be closely aligned with everyday life (EC).
Spatial-visual perception or spatial-constructive abilities	• Children with FASD and visual-spatial dysfunctions, visual impairment should be clinically ruled out by an ophthalmologist. If a visual impairment is present, appropriate aids (e.g. glasses, eye covering) should be prescribed and, depending on the clinical symptoms, visual support should be initiated (EC). • It may be considered to offer individually adapted occupational therapy to the child and practical exercise instructions to caregivers in order to improve the visual-spatial functions of children with FASD (EC).
Executive functions	• Transcranial direct current stimulation (tDCS) ought not to be used solely to improve executive functions in children with FASD (EG: high; RG: B; [22]). • Training aimed at promoting inhibitory control, emotion regulation, and behavior regulation, combined with parent training, ought to be used to enhance executive functions in school-aged children with FASD (EG: moderate; RG: B; [23-25]).
Mathematical skills	• Training to develop arithmetic thinking and skills ought to be used to improve arithmetic abilities in preschool- and school-aged children with FASD. The training should be adapted to FASD and the child's developmental stage (EG: high; RG: B; [26-29]).
Learning and memory skills	• TDCS ought not to be used solely to improve learning and memory in children with FASD (EG: high; RG: B; [22]).

Attention	• Drug therapy recommendations to improve attention in children and adolescents with FASD and ADHD should be based on the guideline "ADHD in children, adolescents and adults"* (EC). • TDCS ought not to be used solely to improve attention in children with FASD (EG: high; RG: B; [22]). • It may be considered using extrinsic reinforcement to support children with FASD in certain areas of attention (EG: low; RG: 0; [30]). • Neurocognitive interventions focusing on self-control and/or attention control strategies ought to be offered to improve attention performance in preschool- and school-aged children with FASD (EG: moderate; RG: B; [26, 29, 31-33]). • It may be considered using parent training in addition to neurocognitive training of the children in order to increase the therapeutic effect on the children's attention performance (EG: moderate; RG: 0; [32, 33]).
Social skills and behavior	• Children with FASD ought to receive social skills training tailored to FASD to increase their knowledge of appropriate social behavior and improve their social skills (EG: moderate; RG: B; [26, 29, 34, 35]). • Neurocognitive training focusing on the development of regulation strategies should be used to improve the behavioral and emotional regulation in children with FASD (EG: high; RG: A; [23, 25, 31-33, 36-38]). • In addition to neurobehavioral and neurocognitive training of children with FASD to improve emotional and behavioral regulation, a therapy attempt with neuroleptics can be considered for severe behavioral disorders. This is an off-label use for most active substances (EC). • Children/adolescents (≥ 6 years of age) with FASD and ADHD should be offered therapy with methylphenidate to improve hyperactivity and impulsivity (EG: high; RG: A; [26, 39, 40]). • Social skills training ought to be supplemented by psychoeducation of parents/caregivers (EG: moderate; RG: B; [26, 29, 34, 35]). • Neurocognitive trainings ought to be supplemented by resource-oriented psychoeducation of parents/caregivers in order to further improve the children's regulation strategies (EG: high; RG: B; [25, 32, 33, 36-38]). • Psychoeducational measures should be offered to parents/caregivers of children with

	FASD to encourage positive behavioral change of the children (EG: moderate; RG: A; [41]). • When providing psychoeducation to parents, their cognitive abilities and any existing neurological and psychiatric disorders (including FASD) should be considered (EC).
Additional recommendations/expert consensus	• Children with FASD should receive pedagogical support tailored to their individual abilities (cognitive abilities, executive functions, social-adaptive abilities and behavioral regulation) in kindergarten and school (EC). • All educators and teachers should receive information regarding fetal alcohol spectrum disorders and strategies adapted to the clinical profile when teaching and interacting with children and adolescents with FASD (EC). • A support and treatment plan that is tailored to the specific needs of the child or adolescent with FASD should be developed, formulated and implemented. This process should involve a collaboration of the legal guardians/parents, FASD-professionals (e.g. doctors or psychologists providing care) and educators/teachers. Additionally, a potential compensation for disadvantages should be considered (EC).

*The guideline is available only in German.

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background:

Attention: There is evidence that high choline intake may improve attention in children with FASD. In order to prevent adverse effects of choline supplementations (e.g. fishy body odor) a choline-rich diet can be used to ensure a sufficient supply of choline for the child.

Before starting drug treatments, all relevant factors (e.g. age, severity of problems, comorbidities, individual needs) must be considered. The treatment must be discussed with the children/adolescents with FASD (if old enough) and their parents/legal guardians and

they must be informed about possible adverse effects. Further, regular monitoring of possible adverse effects and the effectiveness of the treatment must be performed and modified if needed.

Neurocognitive training includes neurobehavioral, cognitive, and behavioral therapies, serious games as well as similar therapeutic modalities targeting domains, such as attention, memory, problem-solving, spatial reasoning, language, interaction, and executive functions. It aims at strengthening neural connections, facilitating the formation of new synapses, and enhancing existing neural networks.

Social skills training is a therapeutic approach focused on improving individuals' ability to interact effectively in social situations. It involves teaching specific social behaviors, communication skills, and interpersonal strategies to enhance social competence, confidence, and relationships.

3.2 Avoidance of adverse effects of the interventions

In the field of preventing side effects of interventions, two expert consensuses have been adopted (Table 2).

Table 2: Recommendations for avoiding adverse effects of interventions in children/adolescents with FASD.

Recommendation/Expert consensus

- Due to potential adverse drug reactions drug therapies ought to be administered to children and adolescents with FASD if pedagogical-psychological treatments (e.g. neurocognitive training) are not sufficiently effective in reducing the CNS functional impairments (EC).
- Drug therapies should be provided under strict medical supervision. When selecting and monitoring drug therapies, the recommendations of the guidelines "ADHD in children, adolescents and adults"* and "Disorder of social behavior"* should be followed, along with the specialist information on the medication (EC).

*The guideline is available only in German.

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: When offering pharmaceutical therapies, FASD as well as the individual needs and comorbidities must be considered as well as possible interactions with other medications.

3.3 Reduction of complications/secondary diseases

The evidence-based recommendations and expert consensuses defined in the guideline for the outcome "Reduction of complications/secondary disorders" are presented in Tables 3 and 4.

Table 3: Recommendations for reducing complications/secondary diseases in children/adolescents with FASD (part 1).

Recommendation/Expert consensus
• To prevent secondary diseases or complications, or at least detect them at an early stage, children and adolescents with FASD should undergo regular pediatric and developmental diagnostic examinations throughout their entire age range, from 0 to 18 years (EC). • Child and adolescent psychiatry should be promptly involved if there are any indications of psychiatric symptoms or risky behavior (e.g. risky alcohol/drug use, self/other endangerment, suicidal acts) in the child/adolescent (EC). • Depending on the clinical symptoms, other specialties should be consulted, such as pediatric subdisciplines, ear, nose, and throat (ENT) specialists, ophthalmology, orthopedics, pediatric radiology, psychotherapy, and others (EC). • To develop effective therapies and interventions for children/adolescents with FASD, these other specialties ought to be integrated into a comprehensive therapy plan, and professional case management ought to be established for each child (EC). • Transparent, interdisciplinary cooperation and the involvement of the children and adolescents themselves, as well as their caregivers/legal guardians ought to be considered throughout the entire support system and therapy period. A stable social environment ought to be created to prevent secondary disorders (EC).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: Compared to the average population individuals with FASD have higher rates of conditions such as psychiatric diseases (incl. addictions), risky behavior, school failure,

delinquency, maltreatment, hospitalization and somatic diseases (e.g., visual disturbances, dizziness, insomnia, headaches, and shortness of breath).

Building on the principles of transparent and interdisciplinary cooperation, it is also essential to incorporate a strengths-based perspective that recognizes and leverages the individual strengths of children and adolescents with FASD, as well as those of their caregivers, throughout the support system and therapy period. By emphasizing individual strengths alongside therapeutic interventions, we can promote a holistic approach that fosters self-efficacy and encourages active participation from children, adolescents, and their caregivers in the therapeutic process.

Table 4: Recommendations for reducing complications/secondary diseases in children/adolescents with FASD (part 2).

Sub-outcome	Recommendation/Expert consensus
Risky behavior	• To reduce risky alcohol consumption in adolescents with FASD, alcohol-preventive neurocognitive training ought to be offered to adolescents, along with psychoeducation for their parents (EG: high; RG: B; [42, 43]). • It may be considered to offer training to reduce risky behaviors to primary school children with FASD in order to increase their knowledge (EC).*
School failure and drop-out	• To ensure positive learning outcomes and prevent school failure or dropout, learning content and environments ought to be tailored to the impairments of children/young people with FASD. If necessary, additional support measures (at school and/or at home) ought to be introduced. Therefore, doctors/psychologists/therapists in charge ought to communicate with the educational staff at school or after-school care, as well as the children/young people, and their guardians, to coordinate educational measures and support integration into existing support programs (EC).

Delinquency	• To prevent delinquent behavior, it may be considered to use neurocognitive training or drug therapies at an early stage to support the child's regulation of emotions and behavior. Since adolescents with FASD often struggle to foresee the consequences of their actions, the consequences of delinquent behavior ought to be explained to them comprehensibly and repeatedly by various professionals as well as close caregivers. Additionally, these explanations ought to be adapted to the individual's learning style and illustrated accordingly. (EC). • The police and judiciary ought to be educated about FASD and informed about the specific characteristics of the individual child/adolescent with FASD. They ought to involve responsible medical professionals and the legal guardians/caregivers in their assessment of delinquent behavior to determine the extent to which age-appropriate capacity for understanding and control is present. This will allow them to judge effectively and fairly in each case (EC).
Maltreatment	• To prevent child maltreatment (as victims or offenders), children and adolescents with FASD ought to be offered early, easily understandable, and repeated education (including sexual education with contraceptive options) as well as strategies for self-assertion and support in interpersonal interactions. In addition, guardians and professionals across the entire support system ought to be informed about the vulnerability of children and adolescents with FASD to child abuse (EC).

*The training should be tailored to the child's developmental stage and aligned with their level of adaptive functioning.

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background:

Risky behavior and delinquency: It is important to recognize that individuals with FASD may face challenges not due to a lack of understanding of rules or situations, but rather due to

brain-based differences that affect impulse control, learning from experiences, and managing high-risk scenarios.

Transition: In adulthood, many individuals with FASD still require support in their daily lives. The transition from pediatricians to psychiatrists/neurologist for adults is important and should be well prepared. The guideline “Transition from Pediatrics to Adult Medicine” (only provided in German) offers general recommendations for a successful transition.

3.4 Improving the participation of children/young people with FASD

Participation was considered a highly relevant outcome by the guideline group. Based on the literature, recommendations and expert consensus were developed for three related sub-outcomes (see Table 5).

Table 5: Recommendations for improving the participation of children/young people with FASD.

Sub-outcome	Recommendation/Expert consensus
Learning and application of knowledge	• If participation in learning and the application of knowledge cannot be sufficiently ensured for a child or adolescent with FASD due to individual cognitive impairments, the need for support from an integration assistant or school companion ought to be assessed, and other appropriate support measures ought to be implemented if necessary (EC). • Professional integration assistants or school companions ought to be familiar with the clinical profile of FASD and its implications for learning, planning, social behavior, and emotional regulation. They ought to be trained in working with children and adolescents with FASD, and the benefits of this support ought to be reviewed regularly (EC). • Adolescents with FASD ought to be offered educational support measures adapted to their cognitive and socio-emotional abilities as part of an individual, needs-oriented support plan coordinated with them and their legal guardians or caregivers (EC).
Domestic life	• For children with FASD, psychoeducation for parents and/or parent-child training ought to be implemented to improve participation in the home environment (EG: moderate; RG: B; [33]). • Legal guardians or caregivers of children and adolescents with FASD ought to be offered educational, psychological, and financial support tailored to the family's needs and the child's impairments to ensure stable care (EC). • If the promotion of development and education of a child/adolescent in the origin, adoptive, or foster family is not (or no longer) possible, forms of pedagogically supported, supervised living adapted to the individual needs and impairments of the child/adolescent

	with FASD ought to be provided. (EC).
Interpersonal interaction and relationships	• For children with FASD, neurocognitive training focusing on self-regulation or social skills ought to be implemented in combination with psychoeducation for parents to improve the child's interpersonal skills and thus participation in the lives of peers (EG: moderate; RG: B; [25, 34]). • Neurocognitive therapies should be offered to children and adolescents with FASD to improve social interaction. These should be adapted to the specific impairments of children with FASD, which are biologically based due to prenatal alcohol-induced brain damage (EC). • These child-centered therapies ought to be supplemented by psychoeducation for legal guardians or caregivers and by intensive education of other caregivers (e.g., educational, therapeutic, and psychological professionals) so that they can develop an understanding of the condition and the child's individual impairments and establish strategies to improve their interactions with the child. (EC).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: Psychoeducation for individuals with FASD, their caregivers, and societal services should consider the brain-based differences of individuals with FASD, focusing on tailored strategies that account for difficulties in impulse regulation and vulnerability management. It is critical to avoid framing individuals with FASD as willfully engaging in maladaptive behaviors, and instead to highlight the importance of structured support systems that address their unique neurodevelopmental needs.

3.5 Improving the quality of life of children/young people with FASD

Even though the improvement of quality of life through interventions was considered a highly relevant outcome by the guideline group, no literature-based evidence was found, and therefore, an expert consensus was formulated (see Table 6).

Table 6: Recommendation for improving the quality of life of children/young people with FASD.

Recommendation/Expert consensus
• Both in the promotion and therapy of children and adolescents with FASD, as well as in the psychoeducation and support of legal guardians and caregivers, the focus ought to be on improving or at least stabilizing the quality of life of the affected children/adolescents and their families (in addition to specific therapy goals based on the individual's impairments) (EC).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: The World Health Organization (WHO) defines Quality of Life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [44].

The systematic literature search identified no publication specifically addressing this topic.

According to subjective reports, forms of animal-assisted interventions can have a positive effect on the quality of life of children and adolescents with FASD and their families. Assistance dogs may improve the quality of life by strengthening social relationships, increasing the child's sense of security, and, thereby, achieving greater independence, as has already been documented with assistance dogs in children with autism spectrum disorders[45-48].

3.6 Relief for caregivers (biological, foster and adoptive parents, other caregivers) and improving the quality of life of the entire family/institution

A guideline recommendation was agreed upon for the quality of life of the entire family, which is linked to parental stress reduction and the fulfillment of family needs (Table 7).

Table 7: Recommendation for creating relief for caregivers (biological, foster and adoptive parents, other caregivers) and for improving the quality of life of the entire family/institution.

Recommendation/Expert consensus
• Parents of children with FASD ought to be offered psychoeducation (if necessary with individual goal-setting) in combination with therapies for the child and family support to reduce parental stress and improve the fulfillment of the family's needs (EG: moderate; RG: B; [37, 38, 49]).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: Long-term support for families adapted to the individual family factors seems necessary to fulfil their needs sustainably.

3.7 Enhancing knowledge of the health condition or disability and fostering insight into the associated challenges

Table 8 presents the guideline group's recommendations and expert consensus for the outcomes “Knowledge enhancement” and “Disease understanding”.

Table 8: Recommendation for enhancing knowledge of the health condition or disability and fostering insight into the associated challenges.

Recommendation/Expert consensus
• Caregivers/legal guardians of children with FASD should be provided with information in group workshops in presence or online information material or written information to improve their knowledge about the condition of FASD (EG: high; RG: A; [41]).
• Legal guardians or caregivers of children with FASD ought to be offered psychoeducation in combination with therapies for the child and family support to improve their knowledge about the condition of FASD in the long term. (EG: moderate; RG: B; [37, 38]).
• When providing psychoeducation to caregivers/parents, we recommend considering their cognitive abilities and any neurological and psychiatric disorders (including FASD) (EC).
• In psychoeducation for legal guardians or caregivers, attention should be paid to their cognitive conditions and any possible neurological and psychiatric disorders (including FASD) (EC).
• Children and adolescents with FASD should be provided with information that is adapted to their developmental stage and cognitive abilities to improve their knowledge about the condition of FASD (EC).
• According to children and adolescents with FASD and their caregivers, the knowledge and communication about their condition or the cause of their impairments often leads to relief. Therefore, research in this area should be conducted. Studies on interventions to improve awareness of the disorder in children and adolescents with FASD are lacking, but they are extremely relevant from a clinical perspective, especially in relation to risky behavior, recognition of support, help-seeking and transition. Therefore, research projects should also be planned in this area (EC).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: Depending on the cognitive abilities of the caregivers, simple language should be used when providing information.

3.8 Improvement in coping and self-efficacy

One guideline recommendation was adopted for the improvement of coping and self-efficacy as an outcome (see Table 9).

Table9: Recommendation for improving coping and self-efficacy in children/adolescents with FASD.

Recommendation/Expert consensus
• Children/adolescents with FASD and their classmates ought to be educated in school about factors of mental health and strategies for coping with health impairments to strengthen the coping skills as well as the self-concept of children/adolescents with FASD (EG: moderate; RG: B; [43]).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: By sharing their personal experiences and talking about FASD, children with FASD can help peers, teachers, and parents in developing a better understanding of the challenges and needs of individuals with FASD. This can reduce prejudice, increase empathy and create an inclusive environment. Thereby, the child's needs must be respected and the voluntariness of the educational work must always be emphasized.

3.9 Additional expert consensus on quality of life, relief of caregivers, knowledge and coping/self-efficacy

Since the guideline group considered quality of life, relief for caregivers, knowledge enhancement, and coping/self-efficacy as highly relevant for the daily lives of children with FASD and their families, additional expert consensuses were adopted in these outcome areas (see Table 10).

Table 0: Additional expert consensus regarding the quality of life, relief of caregivers, knowledge and coping/self-efficacy.

Recommendation/Expert consensus
• The condition of FASD, individual strengths and weaknesses, daily life organization, current issues, and planned therapy content and goals should be communicated and discussed transparently, adequately, and, if necessary, repeatedly with the children and adolescents. When planning therapy, the individual wishes, participation preferences and concerns of children and adolescents with FASD should be taken into account (EC). • Professionals who care for children and adolescents with FASD ought to be familiar with regional and national FASD self-help groups/patient advocacy organizations (EC). • The professionals ought to inform children and adolescents, their legal guardians, and other caregivers about the offerings and support options of self-help (EC). • Caring professionals, health researchers, and patient advocacy organizations/self-help groups ought to collaborate to exchange knowledge and thereby improve the care and quality of life of people with FASD and the affected families (EC).

EG = Evidence grading (low; moderate; high)

RG = Recommendation grading (A – strong recommendation; B – recommendation; 0 – open recommendation)

EC = Expert consensus

Background: Cognitive abilities must be considered when dealing with children/adolescents with FASD, and communication must be adjusted to their developmental level.

4 DISCUSSION

With an estimated prevalence of 1.98 % in the WHO European Region, fetal alcohol spectrum disorder (FASD) represents a significant public health concern[50]. Children diagnosed with FASD encounter a number of challenges that affect their daily functioning and long-term development. The impact of FASD extends beyond childhood and persists into adulthood. Without adequate support and interventions, many children with FASD struggle with everyday situations, preventing them from living independently later in life.

Despite the high prevalence of FASD, there is a lack of studies investigating intervention strategies for children and adolescents with this condition. Particularly concerning are the research gaps regarding enhancing disease management, self-efficacy and quality of life in this population, prompting an urgent need for further investigation.

The assessment of studies found in the systematic literature research was conducted using the GRADE methodology. However, the limited number of available studies in this research field, combined with their heterogeneity in design, outcomes, and interventions, posed significant challenges for standard comparisons and the calculation of effect estimates. Despite these limitations, GRADE provided a structured framework for evaluating the quality of evidence and allowed us to draw evidence-informed conclusions. In areas where there was insufficient evidence, we were unable to formulate evidence-based recommendations. To address these gaps, we relied on expert consensus, drawing on the knowledge and practical experience of professionals in the field. This approach ensures that even in the absence of strong evidence, high-quality, practice-oriented recommendations can be made, reflecting the current state of knowledge and established clinical practice. The inclusion of

expert consensus allows for the formulation of realistic and actionable guidance that is highly relevant in clinical settings.

Existing studies often demonstrate significant qualitative deficiencies. Small study populations hinder sub-analyses of potential confounders such as age, gender or comorbidities[51-57]. Study designs without control groups fail to definitively attribute observed effects solely to the interventions themselves and cannot exclude potentially confounding factors such as test-retest effects, the impact of normal developmental on test results, or the influence of increased attention from study personnel[40, 51, 52, 58]. Additionally, the clinical setting may complicate the transfer of intervention content into real-world settings, leaving the benefits of interventions ambiguous, as children with FASD often suffer from lack in transfer performance due to executive function disorder[58-60]. As some studies examine only a brief intervention period, it is unknown whether extending the intervention duration enhances the therapeutic effect and whether improvements are sustained in the long term[40, 58, 61]. Moreover, the absence of standardized objective assessment tools makes it difficult to evaluate the efficacy of an intervention. Subjective assessments, such as parent or caregiver surveys, may be biased due to their expectations[56, 59, 62-65]. Studies rarely include the perspectives of children or adolescents themselves[66], mainly reflecting parental or caregiver views[52, 62, 65, 67]. This limitation may partly be caused by the cognitive impairments associated with FASD, as affected individuals may lack the cognitive capacity to understand and adequately respond to questions. Additionally, some children may lack the cognitive maturity to assess their situations accurately, hindering their involvement in the research process. However, by tailoring questions to the cognitive developmental level of the

children and addressing individual comprehension issues, children with FASD can be interviewed, as well.

It is essential to note that study populations often include not only children diagnosed with FASD but also those only exposed to prenatal alcohol (PAE)[60, 66, 68], which does not always lead to the development of the clinical picture FASD. Even within children with FASD, significant variability exists due to subtypes (fetal alcohol syndrome [FAS], partial FAS [pFAS], alcohol-related neurodevelopmental disorder [ARND]) and individual differences in the neuropsychological profile, heavily influencing intervention effectiveness. Considering the various number of symptoms and their diverse manifestations, interventions for children and adolescents with FASD should be tailored not only to the disorder itself but also to the strengths and weaknesses of the affected individuals.

Individual therapy sessions provide personalized programs tailored to each child's unique abilities and impairments. Particularly, children with severe functional impairments may benefit more from individual therapies than group sessions, where skill variability often leads to suboptimal outcomes. However, group sessions may be more effective for high-functioning children with FASD, enabling them to practice skills within a social peer context, facilitating integration into daily life.

Beyond the children themselves, parental or caregiver involvement significantly influences intervention effectiveness. Integrating therapy content into family routines profoundly impacts therapy outcomes. Educating caregivers about FASD fosters a deeper understanding of the disorder, creating the framework for providing appropriate support[56, 62-64, 69, 70].

Depending on caregivers' cognitive abilities, appropriate language should be used in the communication process and individual impairments need to be considered.

In conclusion, while intervention studies for children and adolescents with FASD are essential for improving outcomes for affected individuals, numerous methodological and practical considerations must be addressed to enhance the validity and applicability of findings, ultimately optimizing intervention strategies for affected children and their families.

Highlights

- Internationally first evidence-based guideline on interventions for FASD
- Interventions have the potential to improve health outcomes in children with FASD
- Neurocognitive interventions should be adapted to the biological cerebral changes due to prenatal alcohol exposure
- Psychoeducation for caregivers is recommended to improve children’s functioning
- 21 evidence-based recommendations and 26 expert consensus are provided

5 ACKNOWLEDGMENT

We would like to thank all members of the guideline group for their considerable time commitment and professional input (see ePub Table 1).

6 FUNDING

The project on which this publication is based was funded by the Innovation Fund of the Federal Joint Committee (Gemeinsamer Bundesausschuss – G-BA, funding code 01VSF21012). The funding did not influence the development and content of the guideline in any way.

7 CONFLICT OF INTEREST

The authors state no conflict of interest. Neither the study design, collection, analysis, and interpretation of data nor the writing of the manuscript was influenced by the funding bodies.

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Figure 1: Flowchart of the systematic literature search.