Screening Approaches for Detecting Fetal Alcohol Spectrum Disorder in Children, Adolescents, and Adults: A Systematic Review

by

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ABSTRACT

SCREENING APPROACHES FOR DETECTING FETAL ALCOHOL SPECTRUM DISORDER IN CHILDREN, ADOLESCENTS, AND ADULTS

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Identification of fetal alcohol spectrum disorder (FASD) may help facilitate the provision of supports and services for those who need them. Screening has been proposed as an important step in recognizing those at risk of having FASD. The current review aimed to systematically review the literature on screening tools and approaches for the identification of FASD. The search yielded several promising screening tools that are presently available for use with children, adolescents, and adults across a range of settings. Several emerging approaches based on biomarkers associated with prenatal alcohol exposure were also identified in the review. Overall, the current findings suggest that evidence supporting the validity of screening tools and approaches across populations and settings remains limited. Continued research in this area is needed to ensure proper identification of individuals with FASD in order to promote better long-term outcomes. Considerations for the implementation of screening programs are also presented.

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Introduction

Fetal alcohol spectrum disorder (FASD)[1] is a common neurodevelopmental disorder resulting from prenatal alcohol exposure (PAE; Cook et al., 2016; Mattson et al., 2019). Recent studies conservatively estimate 2-5% prevalence in school children in North America, though this is likely an underestimate given limited studies in this area (May et al., 2014; Popova, Lange, Poznyak, et al., 2019; Popova, Lange, Shield, et al., 2019). Prevalence is also estimated to be much higher in vulnerable populations, such as among children in child welfare settings and among those involved in the criminal justice system (Popova, Lange, Shield, et al., 2019). The economic costs associated with FASD are also high. Conservative estimates suggest FASD costs on average $23 804 USD annually per individual with the disorder (ranging from $2 035 - $298 975) in developed countries (Greenmyer et al., 2018). One Canadian study estimated total associated costs to be $1.3 - 2.3 billion annually, with the highest costs resulting from health care, corrections, and productivity loss (Popova et al., 2015).

Individuals with FASD experience wide ranging impairments in their neurodevelopmental functioning, with commonly impacted domains including overall cognitive ability, language, executive functioning, attention, memory, academic difficulties, motor skills, affect regulation, and adaptive behaviour, including social skills and social communication (Cook et al., 2016; Mattson et al., 2019). Compared to the general population, individuals with

[1] While FASD is the diagnostic term currently used according to the Canadian diagnostic guidelines (Cook et al., 2016), other terms have been used to describe individuals impacted by prenatal alcohol exposure, either historically or as part of other diagnostic systems, including fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorder (ARND), fetal alcohol effects (FAE), alcohol related birth defects (ARBD), foetal alcohol syndrome, and foetal alcohol spectrum disorder.

FASD also experience elevated rates of comorbid mental and physical health concerns (Pei et al., 2011; Popova et al., 2016; Reid et al., 2020). Additionally, FASD is associated with high rates of adverse life experiences, including caregiver and school disruption, abuse and victimization, problems with employment, and trouble with the law (McLachlan et al., 2020; Popova et al., 2011; Streissguth et al., 2004). Though many individuals with FASD experience a range of difficulties, with wide ranging inter- and intra-individual profiles, they also have many unique strengths, and achieve healthy and positive outcomes with appropriate supports (Flannigan et al., 2018; McLachlan et al., 2017, 2020).

Earlier recognition, assessment/diagnosis, and provision of individualized intervention services and supports, have been identified as key protective factors that mitigate against the adverse outcomes observed in individuals with FASD (Reid et al., 2020; Streissguth et al., 2004). Formal recognition and/or diagnosis of FASD may confer important benefits, including easier access to appropriate supports, better understanding of the strengths and challenges of the individual, formation of peer and family/caregiver support networks, and improved communication between service providers and individuals with FASD/care providers (Helgesson et al., 2018). However, several barriers to detecting FASD may result in delayed or missed diagnosis. For instance, the relative invisibility of the disorder likely contributes to missed diagnosis, in that only about 10% of those with FASD present with overt outward physical signs of PAE (Astley, 2010; McLachlan et al., 2020). Additionally, confirmation of PAE can be difficult as contact with the birth mother may not be feasible (e.g. children in care; Chasnoff et al., 2015) and because drinking during pregnancy may be underreported due to stigma (Corrigan et al., 2019; Freeman et al., 2019). There is also limited FASD-related knowledge and expertise

among professionals and clinicians to recognize and support individuals with FASD (Brems et al., 2010; Wedding et al., 2007). Owing in part to lack of expertise, as well as the time and cost required for a diagnostic assessment, there is limited capacity to diagnose and address those who may be in need of services (Clarren et al., 2011).

Screening has been proposed as an important step in ensuring that individuals in need of appropriate care and supports are recognized, and in turn, this may result in both improved outcomes and reduction of economic burden associated with FASD (Berrigan et al., 2019). Studies have shown that training healthcare providers to screen for alcohol use in pregnancy, using a range of validated approaches, can promote both critically needed prevention efforts, as well as the early identification of at-risk individuals, thereby providing additional avenues for important intervention services and supports (Jones et al., 2013; Kennedy et al., 2004). Limits to this approach include stigma-driven barriers to disclosure (e.g., Alvik et al., 2006). During the neonatal period, additional screening approaches such as meconium testing have been used as a way to identify newborns with PAE based on alcohol use during the final trimester, thereby increasing opportunities to identify infants and families who may be in need of follow-up supports and intervention (McQuire et al., 2016). While this approach serves an essential purpose, it has narrow application given the brief developmental period during which meconium testing can detect PAE (Goh et al., 2008). To date, evidence-based screening tools for children and adults who may not have been identified during these early stages, but may nevertheless have FASD, are lacking. Efficient and cost-effective screening approaches, validated across ages and settings, may play a critical role in identifying those who may be most at risk and thus most

in need of limited specialized FASD assessment and diagnostic services along with interventions and supports.

In developing and selecting appropriate and evidence-based screening tools, several factors need to be considered. Reliability refers to the ability of a tool to produce consistent results, for example, across multiple administrations or administrators (Litwin, 1995). Validity refers to the ability of a tool to measure the intended construct, in this case, FASD (Litwin, 1995). Several additional metrics are commonly used to evaluate the validity of screening tools. Sensitivity (Se) refers to the ability of a tool to correctly identify true cases, whereas specificity (Sp) indicates the tool's ability to correctly identify true negatives or non-cases (Trevethan, 2017). Positive predictive value (PPV) refers to the probability of being a true case if one were to screen positive, whereas negative predictive value (NPV) refers to the probability of being a true negative if one were to screen negative. Overall accuracy refers to the proportion of screening decisions resulting in correct classification, including both positives and negatives (Maxim et al., 2014). These measures of accuracy are relative to the reference standard, which is a validated approach for classifying true cases and non-cases (Trevethan, 2017). In the case of FASD, best practice for diagnosis involves a multidisciplinary team with specialized training, with multiple guidelines available to support clinical decision making that vary internationally (Coles et al., 2016; Cook et al., 2016). Ideally a screening tool would demonstrate strong psychometric properties, however this is not always feasible and so trade-offs must be considered. For example, a highly sensitive tool will reduce the risk of missed cases, but may also result in reduced specificity, potentially inflating the number of cases to follow-up (i.e. increased risk of false positives). A high false positive rate may not only lead to possible elevated costs and

misuse of limited specialized resources, but may also cause undue stress to individuals and families, particularly in the case of FASD given the stigma associated with the disability (Marcellus, 2007). Alternatively, while increasing specificity may reduce the number of false positives and therefore save on resources, it may also result in missed cases (i.e. increased risk of false negatives), such that some individuals with FASD may not be identified, therefore missing opportunity for support and intervention. Finally, when evaluating screening tools, it is important to consider the population for which the tool has been validated, as screening tools that have been shown to be reliable and valid in one age group or setting may not be appropriate for all populations or across contexts (Goh et al., 2008).

Goh et al. (2008) completed a comprehensive review of FASD screening tools in order to develop a toolkit with multiple approaches to FASD screening. Their review identified several promising tools developed for use in a variety of settings, such as FASD clinics, community, and justice settings. Details regarding many of the reviewed tools was acquired through personal correspondence with the communities and institutions using the tools rather than through searches of published research, suggesting sparse empirical evidence as a limitation at that time. While results of the review suggested that there were a few promising tools in terms of ease of use, administration costs, and level of required administrative expertise, further validation of some of the tools included in the toolkit was recommended. Another review was subsequently conducted in order to update evidence supporting the toolkit (Koren et al., 2014), though only two additional peer-reviewed studies were identified at that time.

While a range of formal and informal screening approaches designed to identify individuals with FASD have been developed and implemented in the field, to our knowledge,

systematic consideration of the evidence-base supporting the utility, reliability, and validity of these tools is lacking. Thus, the aim of this systematic review was to provide an overview of the available evidence relevant to screening for FASD in children, adolescents, and adults across a range of settings. A further objective was to highlight promising screening tools and approaches, including those already developed for practical application, as well as emerging approaches in development, in order to inform best practices in the field. Finally, this review serves to identify gaps in the literature in order to inform areas for future research.

Methods

The current systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was pre-registered with PROSPERO, an international prospective register of systematic reviews (Registration #CRD42019122077).

Inclusion and Exclusion Criteria

The review focused on identifying peer-reviewed empirical (both quantitative and qualitative) evaluations of instruments, protocols, or other tools designed to screen for or detect FASD in a range of settings. Studies were considered for inclusion if: 1) the study focused on screening tools/methods, and/or identification approaches for detecting FASD; 2) the study focused on humans (including children, adolescents, adults, and elder years); 3) the study publication had a title and abstract available in English in the databases searched; 4) the study had undergone academic peer review[2]; and 5) the study offered a novel contribution or new empirical data to the state of the evidence. Studies were not considered for inclusion if they

[2] The peer-reviewed criterion was required for studies identified through databases searches. Studies identified through the grey literature search were not required to have undergone academic peer-review.

focused solely on identifying risk of PAE during the prenatal period in women. Following the initial search and selection of studies a decision was made to exclude animal studies and those that included participants exclusively under five years of age. This decision was made in order to keep the review applied and focused on clinical models during later developmental stages. Additionally, studies that applied tiered approaches or identification strategies, rather than evaluating the efficacy of a single unified tool or approach, such as those commonly described in prevalence ascertainment studies, were also excluded (e.g. May et al., 2014).

Search Strategy

A search of the literature was conducted across seven databases for social sciences and medical research, including: ERIC, CINAHL, Medline, PsycINFO, PubMed, Social Services Abstracts, and Web of Science. Search terms used to identify potential studies included: ("fetal alcohol spectrum disorder*" OR "FASD" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "alcohol related neurodevelopmental disorder*" OR "ARND") AND (screening OR screen OR biomarker OR neurobiomarker OR identification OR detection OR "biological marker*" OR questionnaire OR measure OR instrument). Two overall searches were conducted, including an initial search to identify studies published between January 1st, 1990 and January 11th, 2019, followed by a second search to bring the review up to date by identifying studies published between January 2019 and May 11th, 2020.

A grey literature search was also conducted in parallel to the primary search in order to identify additional screening tools or approaches that may be currently in use in the field but not reflected in the peer-reviewed literature. Four grey literature databases were searched, including:

Open Grey, Open Government Canada, ProQuest, and PsycExtra, using the same search terms.[3] Additional records were identified by searching published proceedings and abstracts from FASD-focused conferences, searching targeted websites based on previous knowledge and recommendations from other grey literature reviews, pulling records from the original search that did not meet the peer-reviewed criteria, searching through reference lists of relevant reviews and publications, conducting searches on Google, and using a custom search engine for Canadian government documents.

All identified studies were uploaded to Covidence, an online software platform for facilitating systematic literature reviews (Veritas Health Innovation, n.d.). All studies were evaluated by at least two independent reviewers based on the study title and abstract. Each study then underwent full-text review by two independent reviewers. Conflicts during the study selection process were resolved through consensus and with input from the senior member of the study team.

Data Extraction

Data relating to population characteristics (e.g. age, setting, ethnicity), study design, and key findings of each study were independently extracted by two members of the research team. Any discrepancies were discussed until consensus was reached.

Quality Assessment

Quality assessment of the evidence of individual studies was completed using the QUADAS-2 framework (Whiting et al., 2011). The QUADAS-2 is a tool designed to evaluate

[3] Due to system constraints, the following search terms were used for Open Government Canada: "("Fetal alcohol spectrum disorder" OR FASD) AND screen".

risk of bias in diagnostic accuracy studies, with precedence for use in screening studies (e.g. Hirota et al., 2018). Typically, the QUADAS-2 also includes assessment of applicability of studies based on whether the study samples match the research question of the review (Whiting et al., 2011). As an example, in a study of interventions for adolescents, applicability might consider the proportion of study samples comprised of adolescents. Given that the current review focused on a wide range of ages groups and intended screening settings, applicability concerns were not evaluated within the QUADAS-2, but rather, were addressed qualitatively.

The Grading of recommendations, assessment, development, and evaluations (GRADE) system is a method of assessing a body of evidence in a systematic review in order to rate the strength of the evidence for making recommendations (Goldet & Howick, 2013). For the current review, the GRADE system was applied to assess the quality of the overall body of evidence towards screening tools/approaches across ages and settings, with a focus on those currently available for use.

Results

Study Characteristics

Figure 1 outlines the study selection process. The initial database search yielded 3010 results after the removal of duplicates and each underwent initial screening at the title and abstract level. Of these, 300 were subsequently selected for full text review, and 26 met final inclusion criteria. The second database search identified 305 records following duplicate removal, all screened at the title and abstract level. Of these, 57 underwent full-text review, and five ultimately met the final inclusion criteria. The grey literature search identified 78 records, of which all were reviewed in full. Nine studies from the grey literature search met final inclusion

criteria, including two peer-reviewed studies. In total, 40 studies were included in the qualitative synthesis, including 33 peer-reviewed studies and 6 additional studies. On review, studies were categorized into three groups, including tools/approaches identified as being currently 'available' for use among individuals with FASD in various age groups and settings, tools/approaches based only on identifying sentinel facial features associated with PAE, and promising emerging approaches. Findings are next reviewed across each of these categories.

Tools/Approaches Available for Use Across the FASD Spectrum

Altogether, the current review identified 10 screening tools or approaches evaluated across 17 studies that could presently be implemented across varied age groups, and populations/settings. Tools applied a variety of formats and administration approaches, including questionnaires, checklists, and/or interviews, and typically focused on neurocognitive, behavioural, and contextual risk factors commonly observed in individuals with FASD. Additionally, some tools in this category included growth factors, such as low height or low weight, as well as sentinel dysmorphic facial features associated with PAE, as part of the screening approach.

Screening Tools Intended for Use with Children in the General Population

Neurobehavioral Screening Tool. Four tools and one general approach were evaluated for use with children. The Neurobehavioral Screening Test (NST) emerged as the most well studied FASD screening tool developed to date, with five studies evaluating its validity and utility (Breiner et al., 2013; LaFrance et al., 2014; Nash et al., 2006; Nash et al., 2011; Patel et al., 2019). The NST is a 10-item questionnaire intended to be completed by parents or caregivers of children and adolescents ages 6-18 years and it takes approximately five minutes to complete

(LaFrance et al., 2014; Nash et al., 2006). NST-items were drawn from the Child Behavior Checklist (Achenbach & Rescorla, 2001) and canvas behaviours commonly associated with FASD. Studies have predominantly demonstrated promising psychometric properties for the NST in identifying individuals with FASD compared to neurotypically developing children. However, using variable and optimal scoring criteria between samples, two studies found somewhat reduced psychometric properties when differentiating children and adolescents with FASD from those with attention deficit/hyperactivity disorder (ADHD; Se = 81% and 89%, Sp = 72% and 54%) compared to differentiating FASD from neurotypically developing children serving as a control group (Se = 86% and 98%, Sp = 82% and 42%; Nash et al., 2006; Nash et al., 2011). Further, one study conducted with children and adolescents found that only one item significantly differentiated those with FASD from those with oppositional defiant disorder (ODD) and/or conduct disorder (CD). Another version of the NST has been proposed for use with children ages 4 to 6 years, using the 7 items with the most relevance for young children from the original NST, which best differentiated those with FASD from neurotypical children in this sample (Breiner et al., 2013). Results of this abbreviated NST demonstrated high levels of sensitivity and specificity. Overall, findings suggest promising utility of the NST as an FASD screening tool, however more research is needed to determine the accuracy of the tool to differentiate FASD from other neurodevelopmental and mental health disorders.

FASD Screening Program. In one peer-reviewed study, Clarren and colleagues (2001) evaluated the feasibility and effectiveness of a general FASD screening program conducted by trained school and public health nurses with children in the first grade in school. Students were referred for follow up if they: a) had at least one of the sentinel facial features of PAE and were

below the 10th percentile in height and/or weight; b) had at least one of the sentinel facial features of PAE and teacher-reported concerns regarding child development or behaviour; or c) family/teacher-expressed interest in having the child assessed and mention of PAE in their school record. The screening program was implemented in several schools across two counties, each with their own consent process. Nearly all eligible participants completed screening using a passive approach to consent (i.e., guardians had to request *not* to have a child complete the screen), while only approximately 25% of all eligible participants completed screening when consent was active (i.e., guardians had to give their consent to have a child complete the screen). Children who screened positive were invited to complete additional assessment for FASD at a diagnostic clinic. Of those who screened positive, 52% received follow-up assessment, and 40% of these were identified as having an alcohol-related diagnosis under the FASD umbrella. Outcomes from the study suggest that widespread screening programs can be implemented within schools by training service providers on screening protocols, resulting in the identification of individuals with FASD, however participation and follow-up rates may be low depending upon the structure of the program.

FAS Screen. The FAS Screen has been evaluated in two peer-reviewed studies to date (Burd et al., 1999; Poitra et al., 2003). The FAS screen is a checklist/self-report tool to be administered by professionals and paraprofessionals who were trained in the procedure. The FAS Screen was initially developed to identify children with FAS[4] specifically, and has been evaluated for use in school settings for children and adolescents. The tool includes items related

[4] FAS is a diagnostic term for individuals with PAE who demonstrate sentinel facial features of PAE along with central nervous system deficits.

to growth impairment (as specified by height, weight, and/or head circumference below the 5th percentile), common behavioural indicators, evidence of intellectual impairment, neurological dysfunction, and facial dysmorphology, as markers of FASD. Cost of screening using the FAS Screen was found to be approximately $13 per child (Burd et al., 1999). Results indicate generally high sensitivity, specificity and accuracy, though PPV was low.

Children's Aid Society of Toronto Screening Tool. One study, identified via the grey literature search, applied the Children's Aid Society of Toronto (CAST) screening tool in a retrospective case review (Steinhart, 2016). The CAST screening tool is a 12-item checklist of personal and familial characteristics thought to be associated with FASD, such as history of domestic violence, family members with a history of alcohol or substance use, physical health concerns or indications of cognitive impairment. Steinhart et al. (2016) reviewed files for children ages 7-15 years in a child welfare setting. Review of each file took roughly 30 minutes. Results indicated that one item significantly differed between children and youth with FASD and without FASD, leading the authors to conclude that their findings did not support wider application of the tool. They also noted that their results may have been impacted by the high occurrence of family risk factors in care settings more broadly.

Fetal Alcohol Behaviour Scale. One peer-reviewed paper evaluating the Fetal Alcohol Behavior Scale (FABS) was identified (Streissguth et al., 1998). The FABS is a self-report checklist, designed to be completed by a caretaker or close other, that aims to identify FASD in individuals from early childhood through adulthood. The FABS includes 36 yes/no questions related to behaviour, emotion regulation, social skills, academic/work performance, and adaptive functioning. Streissguth et al. (1998) conducted their study in five stages in which the FABS was

refined and evaluated for its application for both screening and for predicting long-term outcomes. Data was drawn from a range of samples and settings, including individuals with FASD recruited from diagnostic clinics for research purposes (the reference sample), and individuals without FASD recruited from general practice waiting rooms (the normative sample), as well as adults in corrections. Across the normative and reference samples, the FABS demonstrated high item-to-scale reliability (Chronbach's coefficient $\alpha = 0.91$ and 0.89, respectively). Test-retest reliability was reasonable ($r = .69$) given the length between administrations (range 1.5-9.4 years, $M = 5.0$ years). Of those diagnosed with FAS or FAE in the reference sample, 80% scored above a threshold of 11 or 12. Within a correctional setting, 85% of participants scored below 6 or 7, while 85% of those with FAS or FAE scored above 6 or 7 on the unrefined, 26-item version of the FABS. Further, those who scored higher on the FABS showed increased rates of difficulties, such as being more likely to be living dependently as adults, compared to those living independently. To our knowledge, the FABS has not since been evaluated, leaving little evidence of the efficacy of the tool.

Screening Tools for Adults

Life History Screen. One peer-reviewed study evaluating the Life History Screen (LHS), with respect to FASD, (Grant et al., 2013) was located during the review. The LHS is a screening tool intended to screen broadly for FASD and other neurodevelopmental disorders that may affect outcomes in substance treatment programs. The LHS is a semi-structured interview protocol that includes 27-items spanning daily behaviour, childhood history, maternal alcohol use, employment history, and mental health. The tool is to be administered by the clinician and takes approximately 15 minutes to complete. Grant and colleagues (2013) evaluated whether a

subset of items from the LHS drawn from the Addiction Severity Index (McLellan et al., 1992) interview could differentiate those with possible FASD when integrated within an intake interview for adult women entering addictions treatment (the LHS was not administered in its entirety nor has it been subsequently evaluated). Results indicated reasonable sensitivity though specificity was relatively low, and overall classification accuracy in differentiating those with and without FASD was only slightly better than chance. Considering that evaluation of the LHS in this study included only a subset of the items based on available data, the authors suggest these results are promising. Further research evaluating the entire LHS should be conducted to determine the psychometric properties of the tool.

Structured for Success Project Screening Tool. One study evaluating the Structured for Success Project (SFSP) screening tool was identified via the grey literature search (Wilson, 2006). The SFSP is an initiative aimed at supporting parents who may themselves have FASD. The SFSP screening tool is intended to be completed by a person who knows the individual well, with the aim of identifying parents who may have FASD and thus benefit from SFSP services. The tool consists of 43 items rated using a 5-point scale across multiple domains, including adaptive functioning, interpersonal skills, cognitive abilities, and behavioural challenges. In the identified study, service providers completed the screen based on previously obtained knowledge of one of their clients, a parent with confirmed or suspected FASD. Additional screens were obtained from screening tools which had been previously completed upon entry into the SFSP program. Results indicated high internal consistency (Chronbach's $\alpha = 0.91$) and good test-retest reliability ($r = .748$, $p < .001$), however a lack of reported reference standard underscores the need for additional research to further validate the tool.

Screening in Justice Contexts

Brief Screen Checklist. The Brief Screen Checklist (BSC) was evaluated in three studies, all identified through the grey literature search (Forrester et al., 2015; MacPherson et al., 2011; McLachlan, 2017). Four versions of the BSC were initially developed, including a self-report measure, a version for birth mothers, a version to be completed by collateral informants (e.g. family or friends), and a version for parole officers. However, data was most consistently reported for the self-report version across studies and is thus characterized here. The self-report version of the BSC was developed to screen for FASD in federally incarcerated adults entering an intake and reception centres and included 48 items, rated on either a 5-point Likert scale or dichotomously, spanning three domains, including behaviour, personal history, and maternal use of alcohol and other health behaviours in pregnancy (MacPherson et al., 2011). Minor modifications and refinements to item content were then reported in a study conducted with federally incarcerated women (Forrester et al., 2015). More recently, an abbreviated version of the BSC was also proposed, including 8 yes/no questions drawn from the longer BSC, with findings suggesting promising screening accuracy (McLachlan, 2017). Overall, the studies suggest promising accuracy for the use of the self-report BSC in adult corrections, though estimates of accuracy varied between studies, signifying a need for further evaluation of the tools. Additionally, research is needed on the other versions of the BSC to determine if they may be of use in identifying those with FASD.

FASD Screening and Referral Tool for Youth Probation Officers. The FASD

Screening and Referral Tool for Youth Probation Officers (Conry & Asante, 2010)[5], was evaluated in two studies identified via the grey literature search (McLachlan, 2017; Singal et al., 2018). The tool is designed to be completed by youth probation officers on behalf of their clients with the aim of identifying youth at risk of having FASD. The tool includes a 10-item present/absent checklist of social and personal factors indicative of FASD, and requires approximately 10-15 minutes to complete. The tool is also embedded in a broader referral guide to support case management and referral planning. In one study, retrospective case reviews were conducted for justice-involved youth (ages 12-18 years, n = 323), finding that most charts (n = 215) lacked adequate information to properly complete the screen, resulting in low sensitivity (Singal et al., 2018). Another study applied the tool with justice-involved adults in both community and custodial settings (ages 12-40 years, n = 80). Though probation officers and case managers completed extensive training on the tool, poor utility was observed with high rates of missing data. This, coupled with user feedback, suggested that probation and case management officers working with adults had insufficient knowledge of client developmental and mental health information in order to complete the tool for many clients (McLachlan, 2017). Taken together, there is currently insufficient data to draw firm conclusions regarding the validity and psychometric properties of the FASD Screening and Referral Tool for Youth Probation Officers.

Red Flag Method. The Red Flag Method, a referral screening approach used by the Manitoba FASD Youth Justice Program, was evaluated in one study identified via the grey literature search (Singal et al., 2018). Youth probation officers complete the tool and refer youth

[5] The Screening and Referral Tool for Youth Probation Officers has also been referred to as the Asante FASD Screening Tool and the Asante Centre FASD Screening and Referral Tool

to the FASD program if they demonstrate behaviours and social difficulties indicative of FASD. Singal et al. (2018) used a retrospective case review approach to complete the tool. Though individual psychometric outcomes for the tool were not reported, the authors compared screening outcomes using the Red Flag Method and the FASD Screening and Referral Tool for Youth Probation Officers, finding 70.9% agreement between the two tools. A lack of validated reference standard when evaluating both the Red Flag Method and the FASD Screening and Referral Tool for Youth Probation Officers highlights the need for additional research on these tools.

Initial Risk Screening Measure. The development of the Initial Risk Screening Measure was detailed in one paper identified via the grey literature search (Prediger, 2003). FASD specialists were consulted for feedback regarding items to be included in the screening tool and scoring of the measure, as well as to solicit input concerning general considerations about screening. The tool consists of 15 items, rated on a 5-point scale, across the domains of behaviour, personal history, criminogenic functioning, and history of maternal alcohol consumption. Findings from the current review did not reveal any studies evaluating the tool as of yet.

Screening Based on Facial Features

Six peer-reviewed studies were identified during the search that evaluated screening based on the facial features associated with PAE and FASD. These studies broadly fell in two categories, including those applying manual measurement, and those analysing 2D facial images. While these approaches are currently available for use in clinical contexts, they are reported separately from the other available tools due to exclusive focus on facial dysmorphology. While

these approaches may aid in the recognition of facial features associated with PAE and therefore help to identify some individuals with FASD, relatively few individuals present with identifiable facial features (i.e. ~10%) suggesting restricted application in screening contexts (Astley, 2010; McLachlan et al., 2020). Nevertheless, these approaches have been applied in screening contexts and may prove useful when combined with additional screening tools or referral processes. Additionally, both manual and 2D facial image analysis serve as the foundation of 3D facial image analysis, an emerging approach described later. One key consideration concerning screening based on facial dysmorphology is the role of ethnicity, in that facial differences between ethnic groups may influence facial measurements and classification accuracy (e.g. Moore et al., 2007). As such, where available, screening outcomes across different ethnic groups are considered through this review. However, it should be noted that having representative samples and considering cultural differences is important and speaks to the generalizability of findings for all screening tools.

Manual Measurements. Three peer-reviewed studies evaluating manual measurements of facial features indicative of PAE were identified (Astley & Clarren, 1995; Lee et al., 2016; Moore et al., 2001). Two studies used discriminant analysis of measurements of various facial features to identify those that provided the best classification accuracy distinguishing between children and adults with and without FAS/pFAS in a known-groups design. Findings across these studies suggested sound classification accuracy (Astley & Clarren, 1995; Moore et al., 2001). Another study implemented a screening protocol based on both growth and manual measurement of facial features in high-risk settings, including institutions for children and adolescents with intellectual disabilities, orphanages, and a special education school for children with disabilities

(Lee et al., 2016). Following dysmorphology evaluation of those who screened positive, a small percentage were identified as having FAS,[6] while half were inconclusive (FAS could not be ruled in nor out). Two of the studies were conducted in the United States and reported the ethnicities of their participants as Caucasian (*n* = 176), African American (*n* = 31), Native American (*n* = 15), Alaskan Native (*n* = 7), Asian (*n* = 1), and "other" (*n* = 71; Astley & Clarren, 1995; Moore et al., 2001). The other study was conducted in South Korea and did not specifically report on participant ethnicity (Lee et al., 2016). Given a lack of between group comparisons and conservative sample sizes, results cannot be extrapolated to establish norms across varying ethnicities.

2D Facial Photographic Analysis. Three peer-reviewed studies were identified that used the Facial Photographic Analysis Software, a commercially available tool which involves a computerized analysis of 2D facial images to assess facial features associated with PAE (Astley et al., 2002; Astley & Clarren, 1996; Avner et al., 2014). Across studies, participants ages 0-27 years were represented. Overall, results demonstrated excellent sensitivity (100%) for identifying facial features associated with PAE. Specificity and accuracy were also very high (>99%) in two of the three studies. One study directly compared the manual measurement and the 2D analysis approaches and found mixed classification agreement, with the 2D analysis approach erring on the side of overestimating short palpebral fissure length, ultimately lowering specificity (Avner et al., 2014). Across the two studies which reported the ethnic composition of the sample, the FASD groups included participants who identified as Caucasian (*n* = 36), Black (*n* = 4), Native American (*n* = 6), or another ethnicity (*n* = 3; Astley et al., 2002; Astley & Clarren, 1996).

[6] Based solely on growth and facial indicators, without evaluation of neurodevelopmental/cognitive functioning.

Group comparisons based on ethnicity were not made, and sample sizes of individual ethnic groups were too small to establish norms.

Emerging Approaches: Biomarkers Associated with FASD

The search revealed 17 studies spanning seven approaches best described as emerging due to the preliminary nature of the research and/or because widespread use is not presently feasible. Most are currently at the stage of identifying differences between those with and without FASD and have not yet been evaluated in their ability to differentiate groups. These approaches typically involve specialized equipment and training, and, in some cases, require laboratory testing.

3D Facial Photographic Analysis. 3D facial image analysis is an emerging approach for the detection of facial features of FASD. While some studies provided evidence towards the validity of the technology, other studies are starting to use 3D facial image analysis to identify more subtle facial features resulting from PAE, beyond the traditional sentinel facial features, with the ultimate goal of developing more sensitive tools capable of detecting a larger proportion of individuals across the FASD spectrum. There were six peer-reviewed studies identified in the current review that evaluated computerized 3D facial image analysis (Douglas et al., 2003; Fang et al., 2008; Grobbelaar & Douglas, 2007; Meintjes et al., 2002; Suttie et al., 2013, 2017). Two studies compared manual measurements of eye features associated with FASD to computerized measurement based on 3D photographs and image analysis in young children approximately 6-7 years, finding higher agreement for palpebral fissure length, inconsistent levels of agreement for interpupillary distance, and higher discrepancy for inner canthal distance and outer canthal distance (Douglas et al., 2003; Meintjes et al., 2002). Another study compared manual and

computerized matching of key facial points associated with PAE, finding that most differences fell within an acceptable range (Grobbelaar & Douglas, 2007).

Three studies used full facial scans in order to develop models able to discriminate those with and without PAE/FAS and found high levels of discriminatory accuracy in children and adolescents ages 2-21 years (Fang et al., 2008; Suttie et al., 2013, 2017). Regarding ethnic variation across the samples, one study found that ethnicity influenced which facial measurements best differentiated those with and without FAS (Suttie et al., 2017), while another study also found that psychometric properties varied by ethnic group (Fang et al., 2008). Notably, all six studies were conducted in South Africa. Among the three of that reported ethnicity, participants were either described as Caucasian (n = 331) or Cape Coloured (i.e. South African mixed ancestry; n = 425; Fang et al., 2008; Suttie et al., 2013, 2017).

DNA Methylation. One study looked at DNA methylation, the pattern by which methyl groups are added to DNA molecules, to determine if it could differentiate those with and without FASD (Lussier et al., 2018). The study specifically analysed buccal epithelial cells collected from cheek swabs from a sample of children with FASD 3-18 years of age who were participating in a larger research study. Results demonstrated good sensitivity (91.7%) and promising overall classification accuracy (83.3%). Additionally, the authors tested the algorithm on an independent sample of individuals with autism spectrum disorder (ASD) and reported an absence of evidence of bias based on age, ethnicity, sex, or ASD diagnosis. These results provide evidence suggesting that DNA methylation patterns may be unique to FASD with important screening potential as a biomarker, though further research will be needed to establish feasibility for screening applications.

Insulin Growth Factors. One peer-reviewed study evaluated the concentration of insulin growth factors (IGF) I and II, hormones involved in normal growth, as a potential biomarker of PAE (Andreu-Fernández et al., 2019). Results from a sample of children ages 8-12 years demonstrated differences in IGF-II concentration between those with and without PAE/FASD, with more participants with PAE and even more with FASD falling below the 50^{th} percentile compared to controls. Further, IGF-I levels were correlated with height, weight, and head circumference measures, while IGF-II was associated with several neuropsychological measures. While between group differences were found, it has yet to be determined whether IGF-I and IGF-II can differentiate those with and without FASD.

Dermatoglyphics. Dermatoglyphics, the study of fingerprints and lines of the hand, was evaluated as a potential biomarker of PAE in two peer-reviewed studies (Andreu-Fernández et al., 2020; Planas et al., 2018). One study found that children with the highest levels of fatty acid ethyl esters (FAEE) in meconium samples, a marker of PAE among newborns, also had higher levels of fluctuating asymmetry from the a-b ridge count (FA_{ABRC}) compared to children with lower FAEE levels or non-exposed children (Planas et al., 2018). There were no statistically significant differences in total a-b ridge count (TABRC) in this sample. Another study found significant correlations between FASD diagnosis and TABRC, FA_{ABCR}, total ATD angle, and fluctuating asymmetry of the ATD angle (Andreu-Fernández et al., 2020). Overall, results from these two studies suggest differences in several dermatoglyphic measurements between children with and without PAE/FASD, however more research will be needed to clarify some discrepancies and to determine scoring criteria in order to inform efficient screening application.

Functional Near-Infrared Spectroscopy. One peer-reviewed study evaluated

differences in neural activity between children and adolescents ages 6-18 years with and without PAE using near-infrared spectroscopy, an indirect measure of neural activity that uses near infrared light to detect changes in levels of oxygenated and deoxygenated hemoglobin (Barrett et al., 2019). Results of the study found group differences in the levels of oxygenated and deoxygenated hemoglobin in the left and medial prefrontal cortex during both inhibitory and non-inhibitory conditions of a working memory task. Group differences were also found for oxygenated hemoglobin in the right prefrontal cortex during the inhibitory condition. The authors suggest that these differences may be useful to help differentiate those with PAE from other disorders, however this will require further investigation.

Respiratory Sinus Arrhythmia. One peer-reviewed study explored respiratory sinus arrythmia (RSA), the relation between breathing and heart rate, as a biomarker for FASD (Reid et al., 2019). RSA was measured before and after a mindfulness exercise. While no group differences were found following the mindfulness exercise, there was a trend toward group differences in RSA at baseline, such that the FASD group exhibited lower RSA compared to the non-FASD group. There is currently insufficient evidence to determine whether RSA may prove useful in the identification of FASD.

Eye Movement Control. Five peer-reviewed studies were identified evaluating differences in eye movement control (EMC) as a possible biomarker of FASD. Four studies found group differences on various EMC measures in children and adolescents ages 5-18 years between those with FASD compared to typically developing individuals serving as a control group (Green et al., 2009; Paolozza, Rasmussen, et al., 2014a, 2014b; Paolozza, Treit, et al., 2014). Further, correlations were found between EMC measures and traditional psychometric

tests measuring working memory, visuospatial ability, and inhibition, suggesting that EMC tasks may reflect deficits commonly associated with FASD. A more recent study evaluated a possible screening protocol by determining the optimal combinations of EMC tasks and/or psychometric tests to provide the most efficient and resource effective screening (Zhang et al., 2019). Results suggested that combining only two EMC tasks (the prosaccade task and the natural viewing tasks) yielded the, best balance between classification accuracy (78.3%) and cost-effectiveness ($50 per screen). Adding an additional EMC task (the antisaccade task) along with a short psychometric battery was estimated to require 1.5 hours to complete, cost less than $250, and improved classification accuracy to 84.8%. Taken together, EMC tasks show promise in being able to accurately identify and differentiate those with FASD from neurotypically developing individuals, and could one day be administered by anyone with access to the necessary equipment and appropriate training. While the addition of the psychometric battery requires extra time, cost, and expertise to include as part of the screening protocol, the tests are commonly administered during neurocognitive assessments and therefore may prove a useful addition for screening within a clinical context without a substantial increase in required resources.

Quality Assessment

Results of the quality assessment for studies included in the review using the QUADAS-2 system are presented in Table 2. Overall, studies demonstrated high risk of bias. Across categories, there was high risk of bias introduced in patient selection due to the prevalence of case-control designs. Case-control designs may inflate the estimated sensitivity of tools due to increased risk of including participants who are clearly cases or clearly neurotypical controls (Rutjes et al., 2005). This may be further exacerbated by the fact that most studies recruited

participants with FASD from diagnostic clinics, care settings, and support centers, and may therefore reflect more extreme cases, reducing the generalizability of findings or inflating classification accuracy estimates beyond those settings. Another common source of bias was introduced via flow and timing, such that many studies that relied on diagnostic group as the reference standard only completed diagnostic assessments with those who screened positive and did not otherwise report how "controls" were confirmed as either non-FASD or non-exposed.

Using the GRADE system, the body of literature was also evaluated to determine the strength of the evidence for recommending the use of screening tools and approaches across settings and ages. The GRADE approach was only applied to studies of tools and approaches that were readily available for use, and these were considered separately for those aimed at identifying FASD across the spectrum versus those aimed at detecting the subset of the population with facial features. Studies of emerging approaches were not included in this evaluation as they are not yet ready to be applied to screening. As per the GRADE system, observational studies start with a "low" quality rating and are then upgraded when consistent results are observed by several high-quality studies, downgraded for inconsistency, or when risk of bias is identified (Atkins et al., 2004; Goldet & Howick, 2013). Quality of evidence for recommending screening for across the FASD spectrum, for the range of populations and settings reviewed, was deemed very low at the present time, indicating that estimates of efficacy are uncertain. The very low quality rating was due in part to the risk of bias across studies, as well as the limited number of studies for individual tools (in most cases only 1-2), and the lack of representative samples (e.g., small samples, using primarily neurotypical control groups). While some tools were deemed as having more support than others (e.g. the NST), overall strong

recommendations cannot presently be made for specific screening tools or approaches across settings and ages, highlighting the need for more rigorous research and implementation evaluations. As indicated, screening based on facial features was also deemed very low due to risk of bias based on the QUADAS-2.

Discussion

There is a need for evidence-based screening tools to aid in the identification of individuals with FASD, particularly in high-risk settings where FASD is prevalent. Early identification and intervention are protective factors against various adverse outcomes and promote healthy ones (Reid et al., 2020; Streissguth et al., 2004). While ideally individuals with FASD would be recognized in childhood, identification is frequently missed into adolescence and adulthood, thus validated screening tools are needed across the lifespan (Chasnoff et al., 2015; McLachlan et al., 2020; Pei et al., 2020). The current study thus aimed to systematically review the literature on available and emerging FASD screening tools and approaches in children, adolescents, and adults, across a range of settings. The search yielded various screening tools and approaches, many of which are currently available for use, with others best characterized as emerging approaches that aim to identify biomarkers associated with PAE/FASD. Results highlighted the promising potential of several tools and approaches in terms of their ease of use, cost, and accuracy. However, the overall evidence base is limited and presents with risk of bias, indicating the need for more high-quality research in this area.

For screening for FASD across the full spectrum of the disorder, tools identified in the review included a variety of administration options, including self-report questionnaires, checklists, and interview strategies. Nine such approaches were found for intended use with

children and adolescents, and evaluated across several settings, including schools (e.g., FAS Screen; Burd et al., 1999), and high-risk settings, such as those referred to FASD clinics (e.g., NST; Nash et al., 2006) and in youth corrections (e.g., FASD Screening and Referral Tool for Young Offenders; Conry & Asante, 2010). Three additional tools developed for application with adults were also found, all intended for use in high risk settings, including adult corrections, family support programs, and substance treatment programs. While some of these tools show promising results in terms of their accuracy in differentiating individuals with FASD from neurotypically developing individuals, serious risk of bias was introduced into the estimate of psychometric properties of the tools due to the use of case-control designs and lack of follow up or verification of those who screened negative. Additionally, generalizability of the findings for studies evaluating the psychometric properties and utility of the tools is currently limited given that many of the tools were only evaluated in a single site or in a single sample, and therefore the characteristics of the participants may have been restricted (e.g., ethnicity, socioeconomic status). Further, many of the studies did not include participants beyond those with FASD and groups of neurotypically-developing individuals, therefore findings regarding the accuracy of screening tools may not generalize to more heterogenous populations. Based on the few studies that included participants with other neurodevelopmental disorders, it is likely that tools will show reduced accuracy in practice. Consequently, this may result in an inflated number of positive screens, requiring additional use of limited resources to appropriately follow-up with these individuals and potentially causing unnecessary stress for the individual screened and their families. More high-quality studies are needed using more representative samples, including those with other neurodevelopmental disorders or comorbid conditions, in order to determine the

psychometric properties of the tool, so that practitioners may make evidence-based decisions when selecting a screening tool

A number of studies were identified that evaluated facial features associated with PAE, based either on manual measurements or 2D photographic analysis, in addition to emerging application of 3D analytic approaches. Computerized analysis of photographic images in particular may allow for efficient and objective screening of facial dysmorphology, and the accuracy of these screening approaches is high for detecting the specific facial dysmorphology associated with PAE. However, these approaches will only detect the small proportion of those with FASD who present with facial features. Alternatively, evidence suggests that computerized analysis of 3D facial images is a viable form of measurement and detection of sentinel facial features, and may hold promise in identifying more subtle and nuanced dysmorphic alterations that may be indicative of PAE. By way of limitations, studies included in the present review did not address the viability of these tools in adults. Prior research suggests that while some facial features may persist into adulthood for some individuals, they may diminish with age, and may therefore be more difficult to detect (Moore & Riley, 2015). Taken together, while screening based on facial features may be very effective at detecting facial dysmorphology, these tools are currently limited in their ability to detect all individuals with FASD, particularly those who present without sentinel facial features. As such, these approaches may be most useful when applied in combination with other screening tools, or as a tool to aid in the diagnostic process. Nevertheless, there is emerging evidence towards the use 3D facial analysis for detecting more subtle facial features of PAE which may be capable of detecting a wider proportion of the

spectrum of FASD. However, this line of research is still very preliminary and will require further investigation.

In addition to 3D facial image analysis, the search identified several emerging approaches for detecting of FASD based on potential biomarkers of PAE. Biomarkers have been defined as characteristics that can be measured or evaluated objectively as an indicator of normal or pathogenic processes (Biomarkers Definitions Working Group, 2001). This may prove particularly important in the search for evidence-based approaches to identify individuals with PAE/FASD as early as possible, given the clinical challenges inherent in identifying and diagnosing young children with FASD (McLachlan et al., 2015). As with other potential screening tools for FASD, accuracy, potential for bias, and resource requirements, including cost-effectiveness and level of professional skill required for administration and interpretation of results, must be considered. Advocates of the use of biomarkers suggest that biomarkers may facilitate earlier identification, increase understanding of the disorder, and provide more objective evaluation compared to questionnaires, for example (Mayeux, 2004). Conversely, it has been suggested that biomarkers may be resource intensive for screening, requiring a great deal of time and expertise (Lakhan et al., 2010). Further, biomarkers which rely on cell samples (e.g. DNA methylation) may be susceptible to bias or error as a result of improper storage of the sample or laboratory mistakes (Mayeux, 2004). Indeed, some of the approaches identified in the review, such as analysis of IGF-I/IGF-II and DNA methylation, require laboratory testing, and are therefore vulnerable to the aforementioned concerns. Nevertheless, some of the approaches, such as 3D facial image analysis, dermatoglyphics, and analysis of EMC, may be administered by anybody properly trained in the procedure and use of the equipment. While most of the

approaches included in the review are best considered to be at the preliminary stage of either development or validation, screening based on 3D facial analysis and eye movement control have more ready application potential. However, the studies reviewed presented with serious risk of bias, and there is insufficient information to determine the accuracy of screening tools in heterogenous populations, signifying a need for further research.

Limitations

There are several limitations of the current review. One limitation is a lack of consistency in defining FASD between studies. Since FASD started to appear in the literature in the late 1960s (Jones & Smith, 1973; Lemoine et al., 1968), various diagnostic labels and diagnostic criteria have been proposed, amended, and implemented (e.g. Chudley, 2005; Cook et al., 2016; World Health Organization, 2005). It is therefore possible that the estimated accuracy of the tools may be influenced by when and where the study took place, as well as when and where the participants included in their sample were diagnosed.

Another limitation is that this review does not represent an exhaustive list of available tools and approaches. Some potentially relevant approaches for screening may not have been included in the study as a result of the exclusion/inclusion criteria. For example, it is possible that some screening tools which were studied exclusively with participants under age 5 may have had relevance for older children and adolescents as well. Likewise, the exclusion of animal models may have resulted in missing studies of emerging approaches for detection which could become available for human use in the near future. Further, studies were not included if the approach under investigation did not explicitly indicate that there were screening applications or that they were evaluating a potential biomarker of the disorder. Therefore, studies that looked at

deficits or differences between individuals with FASD and other groups, could potentially have relevance for screening, but would not have been included in the present review. Finally, only studies with abstracts available in English were included in this study. One of the findings of the review was that some tools were not evaluated on representative samples, including ethnically diverse samples. It is possible that some tools may have been evaluated in different countries but would not have been included as they were published in other languages. As such, studies which may have extended the generalizability of the tools to other ethnic or cultural groups may have been missed.

Considerations for Implementing Screening

There are several considerations when determining whether to implement a screening program and how to go about it. The evidence base behind the tool, such as the psychometric properties, the validity, and the reliability of the tool, should be carefully evaluated as there are important drawbacks to misclassifications. False positive results can be expensive and time consuming, as the individual will need to receive proper follow-up, potentially using one of the limited diagnostic assessment slots or inappropriate supports (Maxim et al., 2014). Additionally, false positives may have psychological consequences, not only for the individual but for the family as well, particularly with FASD where a diagnosis implicates the biological mother (Zizzo et al., 2013). On the other hand, false negatives may result in FASD recognition being delayed or missed entirely, meaning that the individual does not receive supports and services which may be beneficial (Maxim et al., 2014). Further, the efficacy of the tool should be considered with respect to the intended population and setting of use. Tools that have demonstrated accuracy in one age group, setting, culture, or set of mental health characteristics,

for example, may not necessarily provide the same accuracy or utility in other contexts (Goh et al., 2008). The resources required to administer screening tools should also be considered. Tools that are expensive to use, require a lot of time to administer, need extensive training for those administering the tool or undertaking screening, involve specialized equipment or laboratory testing, or specialized professionals to determine outcomes, are all factors which may increase costs associated with screening and which may reduce screening capacity or make screening impractical. As such, fewer individuals may be able to be screened, which may result in missed cases.

In addition to appropriate tool selection, careful consideration is needed to identify the intended purposes of screening for FASD, and how results of screening will be followed up. There should be clear goals and outcomes for screening, including how results will be used to inform best practice (Dobrow et al., 2018). If the primary aim of screening is to identify individuals who may benefit from additional evaluation in an FASD diagnostic service, it is important to understand that concern has been raised that regarding limited diagnostic capacity (Clarren et al., 2011). In addition, it is critical that screening tools not become a proxy for proper diagnostic assessment, which may result in inappropriate decisions regarding placement, unsuitable intervention, wasted resources, and undue stress on individuals and their caregivers and families (Goh et al., 2008; Rafoth, 1997). Therefore, as part of the screening program, it is essential to develop a plan for follow-up to support those who screen positive. While ideally this would include an FASD diagnostic assessment, as discussed, diagnostic capacity is limited and may come with long wait-times. There are, however, ways to support individuals awaiting a diagnostic assessment. For instance, while an FASD diagnostic assessment may be pending,

other forms of assessment, such as a medical evaluation for comorbid physical health concerns, psychological or neuropsychological assessments to assess cognitive, academic, adaptive, and mental health functioning, or evaluations by other clinical professionals, such as occupational therapists, can help to identify additional areas of need which could benefit from support. Areas of need that could be targeted for intervention may also be identified through the process of screening itself, regardless of whether or not the individual is identified as at-risk of FASD. For example, there are a number of parent education and training programs which have been applied to various populations, including FASD, resulting in reductions in problematic behaviours (Petrenko & Alto, 2017).

There are also several considerations at the systems level when implementing a screening program. First, it must be decided who will be conducting the screening and how proper training will be ensured. Users of the screening tool must have sufficient knowledge about FASD and training of appropriate administration, not only for the purpose of ensuring accurate screening results, but also to guarantee that screening can be done ethically and safely. This may include training on how to make appropriate inquiry regarding maternal alcohol use, for example, in a way that is compassionate and minimizes stigmatization (France et al., 2010). Being FASD-informed also includes understanding the variety of challenges, deficits, and strengths that individuals with FASD may have, using clear language when communicating, applying a person-centered approach, developing a trusting relationship, and maintaining a trauma-informed lens (Rutman, 2016). Further, there should be a plan for ongoing evaluation of the screening program to ensure the program is meeting the predetermined goals, and to confirm that the benefits of screening outweigh the harms (Dobrow et al., 2018).

Conclusions

Early identification individuals with FASD, coupled with the provision of appropriate intervention and supports, particularly in settings where those with the disability experience additional vulnerability and overrepresentation, play a critical role in decreasing adverse outcomes and promoting healthy ones. However, results from the current review suggest that there is currently no available tool or approach to screen for FASD that is validated across ages and setting. A number of tools and approaches for detecting FASD in children, adolescents, and adults designed for use in particular populations, and settings, such as children in school settings, or adults in criminal justice settings, have been developed and are currently available for use by a range of professionals (e.g., clinicians, teachers). Though some of these available tools show promise regarding their ease of use, cost, ability to differentiate those with FASD, and detect functional deficits and needs that can inform practice modification and accommodations, more research is needed to adequately evaluate their psychometric properties in more representative and heterogenous populations using stronger designs and methodology. While it is important to ensure that evidence is used to inform the selection and implementation of a screening approach, available screening tools and approaches may prove helpful in identifying areas of need that can be addressed through appropriate supports, intervention, and further assessment. Careful consideration must be made when implementing screening programs, including evaluating the suitability of specific tools and implementation outcomes, ensuring training is provided to users and settings so that service providers are FASD-informed, and appropriate follow-up and support for those who are screened as well as their families.

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Table 1

Characteristics and outcomes of studies included in the review

Author/Year/Country	Ages	*N*	% Male	Outcome Screened	Screening Approach or Tool	Recruitment Setting	Outcomes/ Psychometric Properties
Screening Across the Spectrum							
Breiner et al. 2013 (Canada)	4-6y	60	NR	FASD	NST	FASD clinic and previous research participants	Se = 94%, Sp = 96%
Burd et al. 1999 (US)	3-14y	1013	NR	FAS	FAS Screen	Schools	Se = 100%, Sp = 94.1%, PPV = 9.1%, NPV = 100%, Ac = 94%
Clarren et al. 2001 (US)	Grade 1	3740	NR	FASD	Neurobehavioural, growth, and facial indicators	Schools	40% who screened positive and attended a diagnostic clinic were identified as having an alcohol related condition.
Forrester et al. 2015† (Canada)	<35y	23	0	FASD	Brief Screen Checklist – Women	Corrections	Se = 100%, Sp = 82%, PPV = 67%, NPV = 100% Chronbach's α = .94
Grant et al. 2013 (US)	≥18y	549	0	FASD	Subset of the Life History Screen	Community program for women with substance abuse	Se = 80.8%, Sp = 65.5%, LR+ = 2.34, LR- = 0.29, Ac = 67.6%
LaFrance et al. 2014 (Canada)	6-17y	102	44.1	FASD	NST	FASD service program, previous research participants, and community settings	5 item threshold for FASD and controls: Se = 62.5%, Sp = 100%, PPV = 100%, NPV = 64% 5 item threshold for PAE and Controls: Se = 50%, Sp = 100%, PPV = 100%, NPV = 74.4% Trend towards higher sensitivity among adolescents (70.8%) over children (54.2%) 4 Item threshold for FASD and controls: Se = 89.6%, Sp = 90.6%

MacPherson et al. 2011† (Canada)	<30y	91	100	FASD	Brief Screen Checklist	Corrections	Se = 78%, Sp = 85%, PPV = 41%, NPV = 97%, Ac = 84%
McLachlan 2017† (Canada)	18-40y	80	85	FASD	Brief Screen Checklist; FASD Screening and Referral Tool for Youth Probation Officers	Corrections	BSC: Se = 92.3%, Sp = 70.4%, PPV = 44.8%, NPV = 97.4% FASD Screening and Referral Tool for Youth Probation Officers: few items endorsed
Nash et al. 2006 (Canada)	6-16y	90	NR	FASD	NST	FASD clinics, previous research participants, and community settings	FASD and controls: Se = 86%, Sp = 82% FASD and ADHD: Se = 81%, Sp = 72%
Nash et al. 2011 (Canada)	6-18y	220	64.1	FASD	NST	FASD clinics, outpatient treatment centers, and previous research participants	FASD and controls: Se = 98%, Sp = 42% FASD and ADHD: Se = 89%, Sp = 54% FASD and OCD/ODD: one item differed between groups
Patel et al. 2019 (Canada)	3-15y	106	50	FASD	NST	Care settings	Of those who screened positive, PPV = 78%
Poitra et al. 2003 (US)	Kindergarten	1384	NR	FAS	FAS Screen	Schools	Se = 100%, Sp = 95.43%, Ac = 95%
Prediger 2003† (Canada)				FASD	Initial Risk Screening Measure for Young Offenders		Items for the tool were selected base on literature review and experience of professionals
Singal et al. 2018† (Canada)	12-18y	382	NR	FASD	FASD Screening and Referral Tool for Youth Probation Officers	Youth corrections	Se = 34%, Sp = 84%

Steinhart 2016† (Canada)	7-15y	75	57	FASD	Children's Aid Society of Toronto Screening Tool	Care settings	One item differed between the FASD and control groups. Use of the tool was unsupported
Streissguth et al. (1998)	2-51y	739	60.6	FASD	Fetal Alcohol Behavior Scale	Fetal alcohol and drug unit, corrections, and general practice waiting rooms	FASD reference sample, Chronbach's α = .91 Normative sample, Chronbach's α = .89 Test-retest reliability, r = .69 80% of FAS/FAE group had scores about 11 or 12
Wilson 2002† (Canada)	Adults	65	NR	FASD	Structured for Success Project Screening Tool	FASD family support programs	Internal consistency, Chronbach's α .91 Test-retest r = .748*
Screening Based on Sentinel Facial Features							
Astley et al. 1995 (US)	0-10y	194	55.7	FAS	Manual measurement of facial features	FAS clinic	Se = 100%, Sp = 89%, False positive rate = 9%, 71% of false-positives were PFAE
Astley et al. 1996 (US)	0-27y	126	66.7	FAS	Facial Photographic Analysis Software	FAS image database and previous research participants	Se = 100%, Sp = 100%, Ac = 100%
Astley et al. 2002 (US)	0-12y	600	52	FAS	Facial Photographic Analysis Software	Care settings	Se = 100%, Sp = 99.8%, PPV = 85.7%, NPV = 100%, Ac = 99.8%
Avner et al. 2014 (Canada)	2m-15y	40	60	Short PFL and philtrum smoothness	Facial Photographic Analysis Software	FAS clinic	Se = 100%, Sp = 64%
Lee et al. 2016 (South Korea)	4-18y	307	65.5	Facial features	Growth deficiency	High-risk settings	Of those who screened positive, 14.9% met criteria for facial features of FAS, 50.6% were deferred, and 34.5% were classified as No FAS

Moore et al. 2001 (US)	3w-14y	131	58	FAS and pFAS	Manual measurement of facial features	FAS support centres and research centres	PAE vs. Non-PAE: Se = 98%, Sp = 90%, Ac = 96% FAS vs. pFAS vs. controls: Se = 85%, Sp = 94%, Ac = 88%
Emerging Approaches							
Andreu-Fernández et al. 2019 (Spain)	8-12y	150	56	FASD and PAE	Concentration of IGF-I and IGF-II	Previous research participants and adoptees with PAE	Participants with IGF-II concentration below the 5th %ile: FASD = 14%, PAE = 6.5%, Controls = 0% Participants with IGF-II concentration below the 50th %ile: FASD = 43%, PAE = 19.4%, Controls = 3.2% Correlations found between IGF-II and some neuropsychological measures.
Andreu-Fernández et al. 2020 (Spain)	FASD: M = 10.7±3.7y No FASD: M = 12.0±3.4y	185	62.7	FASD	Dermatoglyphics	Previous research participants	Significant correlations found between FASD diagnosis and TABRC, FA_{ABCR}, TATD, and FA_{ATD}.
Barret et al. 2019 (US)	6-18y	71	45.8	PAE	Functional near-infrared spectroscopy	FASD clinics and community settings	Main effect of group found in levels of oxygenated and deoxygenated hemoglobin in the left and medial prefrontal cortex during a working memory task. Main effects of group found in the right prefrontal cortex for oxygenated hemoglobin during the inhibitory condition of a working memory task.
Douglas et al. 2003 (South Africa)	6-7y	46	NR	Facial measurements	3D facial image analysis	Previously collected data	Mean differences between automatic and manual measurements (mm): PFL = 0.66, IPD = 0.27, ICD = 1.19, OCD = 1.17

Fang et al. 2008 (South Africa and Finland)	2.8-21.0y	149	45.6	FAS facial features	3D laser facial scans	Previously collected data	Caucasian: Se = 88.2%, Sp = 100%, Ac = 92.6% Cape Coloured: Se = 91.7%, Sp = 90%, Ac = 90.9% Combined: Se = 82.75% Sp = 76.2% Ac = 80.0%
Green et al. 2009 (Canada)	8-15y	181	46.4	FASD	Eye movement control	Community settings	Group differences between FASD and controls: PS SRT (d = 0.64)*, PS coefficient of variation (d = 0.59)*, PS express saccades (d = 0.07)*, PS direction errors (d = 0.60)*, AS SRT (d = 0.69)*, AS coefficient of variation (d = 0.99)*, AS direction errors (d = 0.92)*
Grobbelaar at al. 2007 (South Africa)	6-7y	48	NR	Facial measurements	3D facial image analysis	Previously collected data	Mean difference between manual and algorithmic marking (mm): PFL = -0.40, IPD = -0.18, ICD = 0.14, OCD = 0.05, ULW = 0.19, ULH = -0.02 95% of differences fell within acceptable limits
Lussier et al. 2018 (Canada)	3.5-18y	229	54.2	FASD	DNA methylation of buccal epithelial cells	Previously collected data and FASD clinics	Se = 91.7%, Sp = 75%, PPV = 90%, NPV = 78.6%, Ac = 83.3%
Meintjes et al. 2002 (South Africa)	Gr. 1	44	NR	FAS facial features	3D facial image analysis	Previously collected data from a community setting	Mean differences between automatic and manual measurements (mm): PFL = 0.1, IPD = 2.9*, ICD = 2.3* Test-retest mean differences (mm): PFL = 0.0, IPD = 0.0, ICD = 0.5*
Paolozza et al. 2014a (Canada)	5-17y	202	49.7	FASD and PAE	Eye movement control	FASD clinics and community settings	FASD performed worse than controls on all psychometric and eye movement measures, including: PS endpoint (d = -0.47)*, antisaccade endpoint (d = -.63, p<.05), and sequence errors (d =-0.86, p<.05). Correlations found between some eye movement tasks and psychometric measures.

Paolozza et al. 2014b (Canada)	5-17y	232	39.7	FASD and PAE	Eye movement control	FASD clinics and community settings	FASD performed worse than controls on all psychometric and eye movement measures: direction errors (d=-0.5), timing errors (d=-0.7); auditory attention (d = 0.6), response set (d = 0.6), Inhibition - naming (d = 0.8), Inhibition – inhibition (d = 1.2), Inhibition – switching (d = 1.4). FASD had negative correlations between direction errors and: inhibition (r = -0.31)*, and switching (r = -0.36)*.
Paolozza et al. 2014 (Canada)	7-18y	78	47.4	FASD	Eye movement control	FASD clinics and community settings	FASD performed worse than controls on: AS SRT (t=2.4)*, AS anticipatory saccades (t=2.4)*, AS direction errors (t=2.8), MGS sequence errors (t=2.1)* and MGS timing errors (t=.9)*
Planas et al. 2008 (Spain)	PAE: M = 9.48y, Controls: M = 9.76y	50	52	PAE	Dermatoglyphics	Hospital setting	Higher FA_{ABRC} levels in those with the highest FAEE compared to low FAEE and non-exposed.
Reid et al. 2019 (Australia)	6-10y	14	47.1	FASD	Respiratory sinus arrythmia	FASD clinic and schools	Trend towards group effects, with lower RSA in the FASD group prior to mindfulness intervention
Suttie et al. 2013 (South Africa)	FAS: M = 10.6$\pm$2.4y pFAS: M = 10.0 $\pm$1.5y HE: M = 10.4$\pm$2.7y Controls: M = 10.1$\pm$2.6y	192	50	Facial dysmorphology	3D facial image analysis	Ante-natal clinics and schools	FAS vs. nonexposed: Ac = 97 – 100% for the face, 92% for the profile FAS/pFAS vs. nonexposed: Ac = 90% for the face, 92% for the profile

Suttie et al. 2017 (US, South Africa, and Europe)	3-18y	415	53.7	Facial dysmorphology	3D facial image analysis	Previously collected data and community settings	Caucasian: Ac = 96% Cape coloured: Ac = 98%
Zhang et al. 2019 (Canada)	5-18y	207	46.9	FASD	Eye movement control and neuropsychological testing	FASD clinics and community settings	PS and natural viewing: Se = 77.27%, Sp = 79.17%, Ac = 78.26% PS, AS, natural viewing and short battery of neuropsychological tests: Se = 81.8%, Sp = 87.5%, Ac = 84.78%

Note. Ac = accuracy, AS = antisaccade, FA_{ABCR} = fluctuating asymmetry from the a-b ridge count, FA_{ATD} = fluctuating asymmetry from the ATD angle, FAEE = fatty acid ethyl esters, FAS = fetal alcohol syndrome, FASD = fetal alcohol spectrum disorder, FP = false positive rate, HE = heavily exposed, ICD = inner canthal distance, IPD = interpupillary distance, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MGS = memory guided saccade, NR = not reported, NPV = negative predictive value, NST = Neurobehavioral Screening Test, OCD = outer canthal distance, PAE = prenatal exposure to alcohol, PFAE = partial fetal alcohol effects, pFAS = partial fetal alcohol syndrome, PFL = palpebral fissure length, PPV = positive predictive value, PS = prosaccade, Se = sensitivity, Sp = specificity, SRT = saccadic reaction time, TABRC = total a-b ridge count, TATD = total ATD angle, ULH = upper lip height, ULW = upper lip width

* $p < .05$ † not peer reviewed

Table 2

Quality assessment of studies using the Quadas-2 framework

Study	Risk of Bias			
	Patient Selection	Index Test	Reference Standard	Flow and Timing
Screening Across the FASD Spectrum				
Breiner et al. (2013)	H	H	L	U
Burd et al. (1999)	H	L	H	H
Clarren et al. (2001)	H	L	H	H
Forrester et al. (2015)	H	H	L	H
Grant et al. (2013)	H	H	H	H
LaFrance et al. (2014)	U	H	U	H
MacPherson & Chudley (2011)	L	H	L	H
McLachlan (2017)	H	H	L	H
Nash et al. (2006)	H	H	L	L
Nash et al. (2011)	H	H	L	U
Patel et al. (2019)	L	L	H	H
Poitra et al. (2003)	L	L	H	H
Prediger (2003)	NA	NA	NA	NA
Singal et al. (2018)	L	L	H	H
Steinhart (2016)	H	H	L	U
Streissguth et al. (1998)	H	H	L	H
Wilson (2002)	H	H	NA	L
Screening Based on Sentinel Facial Features				
Astley & Clarren (1995)	H	H	L	L
Astley & Clarren (1996)	H	H	L	L
Astley et al. (2002)	L	L	H	H
Avner et al. (2014)	H	H	U	L
Lee et al.(2016)	L	L	H	H
Moore et al. (2001)	H	H	L	L
Emerging Approaches				
Andreu-Fernández et al. (2019)	H	H	L	L
Andreu-Fernández et al. (2020)	H	H	L	H
Barrett et al. (2019)	H	H	L	H

Douglas et al. (2003)	U	H	H	L
Fang et al. (2008)	H	L	L	L
Green et al. (2009)	H	H	L	H
Grobbelaar & Douglas et al. (2007)	U	L	L	L
Lussier et al. (2018)	U	H	L	H
Meintjes et al. (2002)	U	L	L	L
Paolozza et al. (2014a)	H	L	L	H
Paolozza et al. (2014b)	H	L	L	H
Paolozza et al. (2014)	H	L	L	H
Planas et al. (2018)	H	L	L	H
Reid et al. (2019)	H	H	L	H
Suttie et al. (2013)	H	H	L	H
Suttie et al. (2017)	H	L	L	L
Zhang et al. (2019)	H	H	L	U

L = Low Risk H = High Risk U = Unclear Risk

Table 3

Quality assessment of screening tools/approaches across settings and ages using the GRADE system

No. of Studies	Study Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality
Screening Across the FASD Spectrum							
18	Low	Serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	No publication bias detected	Very Low
Screening Based on Sentinel Facial Features							
6	Low	Serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	No publication bias detected	Very Low

Figure 1

Flow chart depicting study selection