Biochemistry and Cell Biology
Biochimie et biologie cellulaire

Prevalence of Externalizing Disorders and Autism Spectrum Disorder among Children with Fetal Alcohol Spectrum Disorder: Systematic Review and Meta-analysis

Journal:	*Biochemistry and Cell Biology*
Manuscript ID	bcb-2017-0014.R1
Manuscript Type:	Invited Review
Date Submitted by the Author:	13-Apr-2017
Complete List of Authors:	Lange, Shannon; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Institute of Medical Science Rehm, Jürgen; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Institute of Medical Science; University of Toronto, Dalla Lana School of Public Health; Technische Universitat Dresden, Institute of Clinical Psychology and Psychotherapy & Center of Clinical Epidemiology and Longitudinal Studies Anagnostou, Evdokia; Holland Bloorview Kids Rehabilitation Hospital; University of Toronto, Institute of Medical Science; University of Toronto, Department of Pediatrics Popova, Svetlana; Centre for Addiction and Mental Health, Institute for Mental Health Policy Research; University of Toronto, Dalla Lana School of Public Health; University of Toronto, Institute of Medical Science; University of Toronto, Factor-Inwentash Faculty of Social Work
Is the invited manuscript for consideration in a Special Issue? :	Fetal Alcohol Spectrum Disorder
Keyword:	Autism Spectrum Disorder, Externalizing disorders, Fetal Alcohol Spectrum Disorder, Prevalence, Systematic Review

Prevalence of Externalizing Disorders and Autism Spectrum Disorder among Children with Fetal Alcohol Spectrum Disorder: Systematic Review and Meta-analysis

Shannon Lange[1,2], Jürgen Rehm[1,2,3,4], Evdokia Anagnostou[2,5,6], & Svetlana Popova[1,2,3,7*]

[1] Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, 33 Russell St., Toronto, ON Canada M5S 2S1

[2] Institute of Medical Science, University of Toronto, 1 King's College Cir., Toronto, ON Canada M5S 1A8

[3] Dalla Lana School of Public Health, University of Toronto, 155 College St., Toronto, ON Canada M5T 3M7

[4] Institute of Clinical Psychology and Psychotherapy & Center of Clinical Epidemiology and Longitudinal Studies, Technische Universität Dresden, Chemnitzer Str. 46, D-01187 Dresden, Germany

[5] Holland Bloorview Kids Rehabilitation Hospital Research Institute, 150 Kilgour Rd., East York, ON Canada M4G 1R8

[6] Department of Pediatrics, University of Toronto, 555 University Ave., Toronto ON, M5G 1X8

[7] Factor-Inwentash Faculty of Social Work, University of Toronto, 246 Bloor St. W., Toronto, ON Canada M5S 1V4

***Corresponding author:**

Svetlana Popova, Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, 33 Russell Street, Toronto ON Canada M5S 2S1, e-mail: lana.popova@camh.ca, Tel: 1-416-535-8501 ext. 34558

Abstract

Due to their central nervous system impairments, children with Fetal Alcohol Spectrum Disorder (FASD) commonly exhibit externalizing behaviours such as hyperactivity, impulsivity, and/or delinquency. The purpose of the current study was to estimate the prevalence of neurodevelopmental disorders with prominent externalizing behaviours, namely Attention-Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD), Oppositional Defiant Disorder (ODD), as well as Autism Spectrum Disorder (ASD) among children with FASD. A comprehensive systematic literature search was performed, followed by disorder-specific random-effects meta-analyses. Of the disorders investigated, ADHD was found to be the most common co-morbid disorder among children with FASD (52.9%), followed by ODD (12.9%), CD (7.0%), and ASD (2.6%). When compared to the general population of the United States, these rates are notably higher: 15-times higher for ADHD, two-times higher for ASD, three-times higher for CD, and five-times higher for ODD. The results call attention to the need for identifying a distinct neurodevelopmental profile to aid in the accurate identification of children with FASD and the discrimination of FASD from certain idiopathic neurodevelopmental disorders.

Keywords: Autism Spectrum Disorder; Externalizing disorders; Fetal Alcohol Spectrum Disorder; Prevalence; Systematic Review

Introduction

Prenatal alcohol exposure can result in damage to the brain and other organs of the developing embryo and fetus. A broad range of effects and symptoms caused by prenatal alcohol exposure have been coined under the term Fetal Alcohol Spectrum Disorder (FASD; Cook et al. 2016), which covers the following alcohol-related diagnoses: Fetal Alcohol Syndrome (FAS), Partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), and depending on the diagnostic guideline, Alcohol-Related Birth Defects (ARBD; Chudley et al. 2005; Hoyme et al. 2016). Recently, Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) was included as a condition that warrants further research and also as a specifier for the broader diagnostic term of Other Specified Neurodevelopmental Disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013). ND-PAE is intended to encompass the behavioural, developmental and mental health symptoms associated with prenatal alcohol exposure, and is appropriate for individuals with or without physical findings (Kable et al. 2016).

The unifying outcome for FASD is congenital damage to the central nervous system, which is variably associated with a wide range of mental and behavioural disorders (Burd et al. 2003; Fryer et al. 2007; O'Connor et al. 2002; Popova et al. 2016). The mental and behavioural disorders that occur increase the complexity of care, and can negatively impact the developmental trajectory of these individuals. Especially challenging is that individuals with FASD commonly exhibit externalizing behaviours that are directed toward the external environment and include aggression, anger, defiance, destruction of property, hostility, noncompliance, and violations of social rules. These

problematic behaviours are the core of a group of neurodevelopmental disorders known as externalizing disorders. Externalizing disorders consist of Attention-Deficit Hyperactivity Disorder (ADHD; DSM-5 code: 314.0X; International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code: F90.X), Conduct Disorder (CD; DSM-5 code: 312.8X; ICD-10 code: F91.X), and Oppositional Defiant Disorder (ODD; DSM-5 code: 313.81; ICD-10 code: F91.3). The latter two consist of a persistent pattern of behaviour that include: angry and irritable mood, argumentative and defiant behaviour, and vindictiveness; and aggression, destruction of property, deceitfulness or theft, and serious violations of rules, respectively (American Psychiatric Association 2013). ADHD is characterized by inattention, impulsivity, and hyperactivity (American Psychiatric Association 2013).

Compared to IQ-matched, non-alcohol-exposed peers, it has been found that externalizing behaviours are elevated in children with FASD (Mattson and Riley 2000), who are often described as hyperactive, impulsive, disruptive, and/or delinquent (Nash, et al. 2006). Franklin and colleagues (2008) found that among their sample of children with FASD, 75% scored in the “clinical” range on the externalizing problems scale of the Child Behavior Checklist – a well-established standardized parent/caregiver questionnaire utilized for evaluating social competencies and behavioural problems in children 6 to 18 years of age. However, the presence of externalizing behaviours, whether in the clinical range or not, does not necessarily mean the criteria for a clinical diagnosis has been met.

It is speculated that both postnatal adversity (e.g., impaired parent-child interactions, poor quality of maternal caregiving, placement in foster care) and prenatal

alcohol exposure are significant predictors of externalizing behaviour in children with FASD (Rodriguez et al. 2009; Staroselsky et al. 2009). Prenatal alcohol exposure significantly increases the risk of postnatal adversity, making alcohol-exposed children inherently vulnerable to developing externalizing behaviours.

In addition to their behavioural impairments, children with externalizing disorders often have problems with their social and academic functioning. Although not an explicit externalizing disorder, Autism Spectrum Disorder (ASD; DSM-5 code: 299.00; ICD-10 code: F84.0) is associated with high rates of externalizing behaviours (Mahan and Matson 2011; Totsika et al. 2011). Children with ASD tend to have more severe externalizing behaviors such as poor attention, disruptive, hyperactive, delinquent and aggressive behaviors than typically developing children and children with intellectual disability (Brereton et al. 2006; Bauminger et al. 2010; Matson et al. 2009).

Given that externalizing behaviours are elevated in children with FASD, it is likely that rates of disorders with prominent externalizing behaviours are also elevated. Therefore, the aim of the current study was to estimate the prevalence of ADHD, ASD, CD, and ODD among children with FASD, and compare the prevalence of these disorders among children with FASD to the prevalence among the general population (i.e., children without FASD).

Materials and Methods

To begin, a comprehensive systematic literature search was performed to identify all existing studies that have reported the prevalence of ADHD, ASD, CD, and/or ODD

among children with FASD. Then, disorder-specific random-effects meta-analyses on prevalence were conducted.

Comprehensive systematic literature search

A comprehensive systematic literature search was performed to identify all studies that have reported the prevalence of ADHD, ASD, CD, and/or ODD among a sample of individuals with FASD. The search was conducted in multiple electronic bibliographic databases, including CINAHL, Embase, ERIC, Medline (including Medline In-Process), PsycINFO, Scopus, and Web of Science (including Science Citation Index, Social Sciences Citation Index, and Arts and Humanities Citation Index). The search was conducted using the following keywords: 1) alcohol embryopath*, alcohol* related* birth defect*, alcohol related neurodevelopmental disorder, arbd, arnd, fae, fas, fasd, fetal alcohol effect*, fetal alcohol syndrome, fetal alcohol spectrum disorder*, foetal alcohol effect*, foetal alcohol syndrome, foetal alcohol spectrum disorder*, partial fetal alcohol syndrome, partial foetal alcohol syndrome, pfas, prenatal* alcohol expos*, OR pre-natal* alcohol expos*; AND 2) frequenc*, incidence*, occurren*, prevalence*, OR rate*; AND 3) add, adhd, attention deficit disorder*, attention deficit hyperactivity disorder, autism, autism spectrum disorder*, conduct disorder, externalizing disorder*, OR oppositional defiant disorder; AND 4) cohort stud*, cross* sectional stud*, prospective cohort stud*, OR retrospective cohort stud*.

The search was not limited geographically or by language of publication, and was performed to identify all studies published from November 1973 (when FAS was first described; Jones and Smith 1973) up to the end of September 2016. The search was

limited to human studies in all databases that allow for this restriction to be specified. Manual reviews of the content pages of the major neurodevelopmental disorders/behavioural journals, as well as citations in any of the relevant articles, were conducted. The full review protocol is available in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/), registration number CRD42016052041.

Inclusion and exclusion criteria

Articles were retained if they i) consisted of original, quantitative research published in a peer-reviewed journal; ii) included subjects with diagnosed FASD or any of the diagnostic entities that fall within the spectrum (ARBD, ARND, FAS, and pFAS); and iii) reported the prevalence of diagnosed ADHD, ASD, CD, and/or ODD among a sample of individuals with diagnosed FASD with a) a measure of uncertainty (confidence interval [CI] or standard error), or b) either the sample size or number of cases. Articles were excluded if they i) reported a pooled estimate by combining several studies (i.e., meta-analysis), or ii) were published in iteration (i.e., dual publications). In cases where more than one study used the same dataset or cohort (or there was an overlap in samples), the study with the larger sample size was retained.

Data selection and extraction

Study selection began by screening titles and abstracts for inclusion. Then, full-text articles of all studies screened as potentially relevant were considered. Two investigators conducted each study selection step; any disagreements were reconciled by team discussion. All data was extracted by one investigator and then independently

crosschecked by a second investigator; all discrepancies were reconciled by team discussion. Effort was made to contact the corresponding author of studies where data was either missing or not reported due to small cell counts or there were discrepancies in the data reported.

Critical appraisal of existing studies

Each study was critically appraised using a tool specifically for use in systematic reviews addressing questions of prevalence (Munn et al. 2014). The following ten criteria were used: i) representativeness of the sample; ii) appropriate recruitment of participants; iii) adequate sample size (n≥100); iv) participants and setting described in detail; v) sufficient coverage of the identified sample; vi) use of an objective, standard criteria for measuring the condition; vii) reliability of condition measurement; viii) appropriateness of statistical analysis; ix) identification and accounted for confounders/subgroups/differences; and x) adequate response rate (>70%). Two investigators independently appraised the quality of each study, and all discrepancies in quality ratings were reconciled by team discussion.

Meta-analysis

In order to estimate the pooled prevalence for ADHD, ASD, CD, and ODD among children with FASD, disorder-specific random-effects meta-analyses (DerSimonian and Laird 1986) were performed. As recommended for meta-analyses of prevalence and to prevent the overweighting of studies reporting extremely low prevalence (i.e., a prevalence approaching zero; Barendregt et al. 2013; Rücker et al. 2009), the data were

transformed using the Freeman-Tukey double arcsine transformation (Freeman and Tukey 1950). Score test-based confidence intervals (CI) were estimated for each study specific point estimate, and Wald-type CI were estimated based on the approximate normal distribution of the transformed pooled point estimates. The resulting combined point estimates and respective CI were back-transformed and presented in forest plots. Given that the conceptualization of ADHD, ASD, CD, and ODD has changed over the years, studies were ordered by year of publication in the forest plots in order to explore whether a temporal relationship was likely to exist. Heterogeneity between double arcsine-transformed estimates of ADHD, ASD, CD and ODD was assessed using the I^2 statistic (Higgins and Thompson 2002). Publication bias was examined by visually inspecting the funnel plot (standard error plotted against the point estimate) for a skewed distribution, and by employing Egger's weighted regression test for small-study effects (Egger et al. 1997). It was decided a priori that i) if publication bias were present it would not be adjusted for, since it was assumed that the prevalence estimates of interest would likely be published even if substantially different from previously reported estimates; and ii) if heterogeneity was present, the following sub-analyses would be conducted: disorder-specific meta-analyses by a) population (general vs. special populations) and b) method of case ascertainment (active vs. passive). All meta-analyses were performed using Stata version 14.2.

Comparison of the prevalence of ADHD, ASD, CD, and ODD among children with FASD to the prevalence among those without FASD

The prevalence estimates of ADHD, ASD, CD, and ODD among children with FASD were compared to the prevalence of these disorders among the general population of the United States, obtained from the available literature.

Results

Comprehensive systematic literature search

Initially, the electronic search yielded a total of 931 articles and six articles were identified through the manual search. After removing 379 duplicate articles, a total of 558 articles were screened using titles and abstracts. One hundred and forty-three full-text articles were retrieved for further consideration, 123 of which were subsequently excluded. Twenty articles were identified and included in the meta-analyses. It should be noted that one article that reported an extremely high prevalence of ASD among children with FASD (76.2%; Mukherjee et al. 2011) was excluded as it was conducted among a highly selected non-random group of individuals referred to a specialist psychiatric neurodevelopmental clinic. A schematic diagram of the search strategy is depicted in Figure 1.

- Insert Figure 1 about here -

Twenty studies reported the prevalence of ADHD among a total of 2,582 children with FASD, six studies reported the prevalence of ASD among a total of 1,029 children with FASD, five studies reported the prevalence of CD among a total of 1,514 children with FASD, and 11 studies reported the prevalence of ODD among a total of 2,719

children with FASD. The mean age of the participants in the identified studies ranged from 6.2 to 22.0 years, and the percentage of males in the samples ranged from 41.9% to 78.3%. Thirteen of the studies utilized passive methods of case ascertainment (e.g., surveys, medical charts) and seven studies actively assessed the study participants' neurodevelopmental status. Fifteen studies were conducted among a sample drawn from the general population, two studies were among an Aboriginal population, and three studies were conducted among children in care (e.g., children in foster care, orphanage). Only seven of the studies reported the diagnostic criteria used when diagnosing the disorders of interest (ADHD, ASD, CD, and ODD), while 17 studies explicitly stated the criteria used for ascertaining cases of FASD. See Table 1 for the study characteristics and the prevalence of ADHD, ASD, CD, and ODD among individuals with FASD reported in the individual studies.

- Insert Table 1 about here -

Critical appraisal of existing studies

Eighteen studies (90%) utilized a sample representative of the target population; 20 studies (100%) recruited study participants in an appropriate way; 5 studies (25%) had an adequate sample size (n≥100); 14 studies (70%) described the participants and setting in detail; 11 studies (55%) had sufficient coverage of the identified sample; seven studies (35%) used an objective, standard criteria for measuring the disorders of interest (ADHD, ASD, CD, and ODD); 15 studies (75%) measured the disorders of interest (ADHD, ASD, CD, and ODD) in a standardized way; 19 studies (95%) conducted an appropriate

statistical analysis of the data; 13 studies (65%) identified and accounted for confounders/subgroups/differences; and eight studies (40%) of studies had an adequate response rate.

Meta-analysis

Pooled prevalence of ADHD, ASD, CD, and ODD among children with FASD

The results of this meta-analysis revealed that ADHD had the highest prevalence among children with FASD (52.9%; 95% CI: 43.7%–62.0%), followed by ODD (12.9%; 95% CI: 8.4%–18.2%), CD (7.0%; 95% CI: 2.5%–13.2%), and ASD (2.6%; 95% CI: 1.4%–4.14%; Table 2). For the forest plots of the prevalence of ADHD, ASD, CD, and ODD among children with FASD see Figure 2.

- Insert Table 2 about here -

- Insert Figure 2 about here -

The tests of heterogeneity demonstrated that heterogeneity was present in the estimates of ADHD, CD, and ODD (I^2=94.6% for ADHD, I^2=80.8% for CD, and I^2=89.0% for ODD; Table 2). Further, according to the funnel plots and Egger's weighted regression test, there was evidence for the presence of publication bias in the meta-analyses of ADHD, ASD, and ODD (*P*=0.000 for ADHD, *P*=0.025 for ASD, and *P*=0.046 for ODD; Table 2). For the funnel plots of the prevalence of ADHD, ASD, CD, and ODD among children with FASD see Figure 3.

- Insert Figure 3 about here -

Sub-analyses

Neither population or method of ascertainment were determined to be sources of heterogeneity in the disorder-specific estimates where heterogeneity was found to be present (i.e., ADHD, CD, and ODD). See Table 3 for the results of the disorder-specific meta-analyses by population and by method of case ascertainment.

- Insert Table 3 about here -

Comparison of the prevalence of ADHD, ASD, CD, and ODD among children with FASD to the prevalence among those without FASD

The prevalence among the general population of the United States was reported to be 4.1% for ADHD (versus 52.9% among children with FASD; Kessler et al. 2005), 1.5% for ASD (versus 2.6%; Christensen et al. 2016), 2.7% for CD (versus 7.0%; Costello et al. 2003), and 2.7% for ODD (versus 12.9%; Costello et al. 2003). See Figure 4 for the prevalence of ADHD, ASD, CD, and ODD among children with FASD and without FASD (i.e., the general population).

- Insert Figure 4 about here -

Discussion

The current study revealed that, of the disorders investigated, ADHD was the most common co-morbid disorder among children with FASD (52.9%), followed by ODD (12.9%), CD (7.0%), and ASD (2.6%). These rates are notably higher compared to the general population of the United States: 15-times higher for ADHD, two-times higher for ASD, three-times higher for CD, and five-times higher for ODD (Christensen et al. 2016; Costello et al. 2003; Kessler et al. 2005). Based on a population of 73.6 million children and youth (0-18 years of age; U.S. Census Bureau 2016) and an FASD prevalence of 1.5% among the general population (Popova et al. 2017), it is estimated that there were 1.1 million children and youth with FASD in the United States in 2016. As per the results of the current study, 592.1 thousand children and youth with FASD in the United States will have a co-morbid diagnosis of ADHD, 144.4 thousand will have a co-morbid diagnosis of ODD, 78.4 thousand will have a co-morbid diagnosis of CD, and 29.1 thousand will have a co-morbid diagnosis of ASD. These staggering numbers highlight the burden that FASD has on the mental health care system. To attest to this, it was estimated that the cost for psychiatric care hospital days associated with a diagnosis of FAS in Canada in 2008–2009 was approximately $1.2 million (Popova et al. 2012).

However, the extent of the relation between FASD and the examined neurodevelopmental disorders (ADHD, ASD, CD and ODD) may be inflated due to two main reasons: i) overlapping diagnostic criteria, and ii) referral bias (McLennan 2015). First, currently, there are a number of clinical guidelines for diagnosing FASD (e.g., Astley 2004; Chudley et al. 2005; Hoyme et al. 2016; Landgraf et al. 2013; Watkins et al. 2013), and although there is considerable overlap in the current criteria, there are also notable differences. The general lack of consensus in the operationalization of the

diagnostic criteria of FASD and especially on the pathognomonic behavioural manifestation of prenatal alcohol exposure and/or FASD has resulted in the overlapping of the diagnostic criteria for FASD with that of other neurodevelopmental disorders among children who were not exposed to alcohol prenatally or for whom prenatal alcohol exposure is not etiologic (McLennan 2015).

Second, FASD research typically relies on clinically-referred samples. This is problematic given that children and youth with obvious disruptive behaviours are more likely to get referred to a specialized FASD diagnostic clinic than those without such behaviours. Further, clinical populations are likely to be much more severely impaired and have crossed a threshold where parents or caretakers are seeking help. Thus, relying on clinically-referred samples to determine the prevalence of neurodevelopmental disorders with prominent externalizing behaviours is likely to result in inflated estimates (McLennan 2015). Therefore, it is necessary to investigate the prevalence of co-morbid neurodevelopmental disorders among children with FASD in non-referred samples (i.e., population-based samples). In addition, adverse life outcomes such as parental abuse and substance use could be the reason for the referral to a diagnostic clinic, which could have predisposed the child to mental health problems (Streissguth et al. 2004); thus, potential confounders need to also be considered.

Regardless, whether it is due to the diagnostic overlap or true co-morbidity, children with FASD often receive multiple diagnoses before they are appropriately assessed and diagnosed with FASD (Chasnoff et al. 2015). To attest to this, Chasnoff and colleagues (2015) found that ADHD was the most common referral diagnosis for children who ultimately were diagnosed with FASD. Alarmingly, misdiagnosed children are often

prescribed inappropriate medications and receiving therapies that are not necessary (Chasnoff et al. 2015). Another reason for the misdiagnosis of children with FASD is stigmatization – the diagnosis of an externalizing disorder is less stigmatizing as compared to FASD and therefore, they are preferentially used by health care practitioners (Elliott et al. 2006; Payne et al. 2005).

Misdiagnosis of FASD (and in general) has a number of consequences, namely implications for the pharmacologic and therapeutic approach to treatment, mismanagement of behavioural symptoms, inaccurate incidence and prevalence estimates, and reduced power to detect a clinically meaningful difference between groups in clinical research studies (Astley and Clarren 2000; Chasnoff et al. 2015). As such, this study highlights the need for teratological history to be sought for all children with any neurodevelopmental disorder (especially externalizing disorders) in order to enhance the differential diagnostic process and provide an accurate and appropriate diagnosis. Further, health care providers need to routinely consider prenatal alcohol exposure in the differential diagnosis of behavioural problems.

An early and accurate diagnosis of FASD is essential, as it can lead to early participation in targeted developmental interventions, which can ultimately improve the child's quality of life and lead to a more prosperous developmental trajectory in terms of social functioning. Early and accurate diagnosis is also important for parents/caregivers. It provides them with an explanation for the behavioural problems exhibited and can improve parenting by increasing their understanding of the child's disabilities and impairments, and can result in more realistic expectations for the future. However,

diagnosis is only useful if the necessary interventions are made available to the affected child.

It is important to acknowledge that externalizing behaviours exhibited by children with FASD can be considered either a response to or an impairment caused by the brain damage that is due to the exposure to alcohol prenatally. This distinction is important in terms of intervention, as behaviours can often be modified by behaviour management, whereas impairments can be managed by accommodations (Paintner et al. 2012). Additional research is this area is needed. However, the co-occurrence of the examined neurodevelopmental disorders (ADHD, ASD, CD and ODD) and FASD represent many complex cases, and deserve timely and tailored intervention.

The current study has a number of strengths such as, the comprehensive search strategy, strict inclusion and exclusion criteria, critical appraisal of studies included in the meta-analyses, and identification of dual publications (thereby avoiding any potential of double counting cases). However, there are a few limitations worth noting. First, as stated above, FASD research studies typically rely on clinically-referred samples, and the studies included in the current investigation are no exception. Second, small sample sizes remain a common limitation in the field of FASD research, and the majority of studies (75%) included had a sample size below 100 participants. Third, very few (six) studies included explicitly stated the criteria used for identifying cases of ADHD, ASD, CD, and ODD. Fourth, the conceptualization of ADHD, CD, ODD and especially ASD has changed over the years, which was not possible to control for in the current study. However, as per the forest plots, a temporal relationship does not appear to be present for any of the disorders of interest (i.e., ADHD, ASD, CD, and ODD).

Nevertheless, the results call attention to the need for identifying a distinct neurodevelopmental profile, which would aid in the accurate identification of children with FASD and the discrimination of FASD from certain idiopathic neurodevelopmental disorders. In addition, a neurodevelopmental profile, that is pathognomonic of FASD, will have important clinical implications by assisting in the ascertainment of accurate prevalence estimates, planning/development of appropriate targeted interventions, and enhancement of clinical services to children, adolescents and adults with FASD. Additional research in this area is needed, as it is possible that individuals with FASD exhibit more than one neurodevelopmental profile.

To conclude, the results of the current study should not be misused for the further stigmatization of children with FASD. Rather, they should be used as strong scientific evidence demonstrating to clinicians working with children the complexity of FASD and the large portion of children with FASD that meet the criteria for other neurodevelopmental disorders.

Acknowledgements

The authors would like to thank Dr. Raja Mukherjee for his thoughtful comments on the first draft of this article.

References

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders, 5th edition: DSM-5. American Psychiatric Association, Washington, DC.

Astley, S.J. 2004. Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. Third Edition. University of Washington Seattle, Washington DC.

Astley, S.J. 2010. Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network. Can J Clin Pharmacol. **17**(1): e132–e164.

Astley, S.J., and Clarren, S.K. 2000. Diagnosing the full spectrum of fetal alcohol-exposed individuals: Introducing the 4-digit diagnostic code. Alcohol Alcohol. **35**(4): 400–410.

Barendregt, J.J., Doi, S.A., Lee, Y.Y., Norman, R.E., and Vos, T. 2013. Meta-analysis of prevalence. J Epidemiol Community Health. **67**: 974–978.

Bauminger, N., Solomon, M., and Rogers, S. J. (2010). Externalizing and internalizing behaviors in ASD. Autism Res. **3**(3): 101–112.

Bell, S.H., Stade, B., Reynolds, J.N., Rasmussen, C., Andrew, G., Hwang, P.A., and Carlen, P.L. 2010. The remarkably high prevalence of epilepsy and seizure history in fetal alcohol spectrum disorders. Alcohol Clin Exp Res. **34**(6): 1084–1089.

Burd, L., Klug, M.G., Martsolf, J.T., and Kerbeshian, J. 2003. Fetal alcohol syndrome: neuropsychiatric phenomics. Neurotoxicol Teratol. **25**(6): 697–705.

Brereton, A.V., Tonge, B.J., and Einfeld, S.L. 2006. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord. **36**(7): 863–870.

Centers for Disease Control and Prevention (CDC). 1995. Update: trends in fetal alcohol syndrome--United States, 1979-1993. MMWR Morb Mortal Wkly Rep. **44**(13): 249–251.

Chasnoff, I.J., Wells, A.M., and King, L. 2015. Misdiagnosis and missed diagnoses in foster and adopted children with prenatal alcohol exposure. Pediatrics. **135**(2): 264–270.

Chen, M.L., Olson, H.C., Picciano, J.F., Starr, J.R., and Owens, J. 2012. Sleep problems in children with fetal alcohol spectrum disorders. J Clin Sleep Med. **8**(4): 421–429.

Christensen, D.L., Baio, J., Braun, K.V., Bilder, D., Charles, J., Constantino, J.N. et al. 2016. Prevalence and characteristics of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring Nnetwork, 11 Sites, United States, 2012. MMWR Surveill Summ. **65**(No. SS-3): 1–23.

Chudley, A.E., Conry, J., Cook, J.L., Loock, C., Rosales, T., and LeBlanc, N. 2005. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ. **172**(5 suppl): S1–S21.

Clark, E., Lutke, J., Minnes, P., and Ouellette-Kuntz, H. 2004. Secondary disabilities among adults with fetal alcohol spectrum disorder in British Columbia. J FAS Int. **2**(13): 1–12.

454 Cook, J.L., Green, C.R., Lilley, C.M., Anderson, S.M., Baldwin, M.E., Chudley, A.E., et
455 al. 2016. Fetal alcohol spectrum disorder: a guideline for diagnosis across the
456 lifespan. CMAJ. **188**(3):191–197.
457 Costello, E.J., Mustillo, S., Erkanli, A., Keeler, G., and Angold, A. 2003. Prevalence and
458 development of psychiatric disorders in childhood and adolescence. Arch Gen
459 Psychiatry. **60**(8): 837–844.
460 DerSimonian, R., and Laird, N. 1986. Meta-analysis in clinical trials. Control Clin Trials.
461 **7**(3): 177–188.
462 Egger, M., Smith, G.D., Schneider, M., and Minder, C. 1997. Bias in meta-analysis
463 detected by a simple, graphical test. Br Med J. **315**(7109): 629–634.
464 Elgen, I., Bruaroy, S., and Laegreid, L.M. 2007. Lack of recognition and complexity of
465 foetal alcohol neuroimpairments. Acta Pædiatr. **96**(2): 237–241.
466 Elliott, E.J., Payne, J., Morris, A., Haan, E., and Bower, C. 2008. Fetal alcohol syndrome:
467 a prospective national surveillance study. Arch Dis Child. **93**(9): 732–737.
468 Elliott, E.J., Payne, J., Haan, E., and Bower, C. 2006. Diagnosis of foetal alcohol
469 syndrome and alcohol use in pregnancy: A survey of paediatricians' knowledge,
470 attitudes and practice. J Paediatr Child Health. **42**(11): 698–703.
471 Franklin, L., Deitz, J., Jirikowic, T., and Astley, S. 2008. Children with fetal alcohol
472 spectrum disorders: problem behaviors and sensory processing. Am J Occup Ther.
473 **62**(3): 265–273.
474 Freeman, M.F., and Tukey, J.W. 1950. Transformations related to the angular and the
475 square root. Ann Math Stat. **21**(4): 607–611.

476 Fryer, S.L., McGee, C.L., Matt, G.E., Riley, E.P., and Mattson, S.N. 2007. Evaluation of
477 psychopathological conditions in children with heavy prenatal alcohol
478 exposure. Pediatrics. **119**(3): e733–e741.
479 Green, C.R., Mihic, A.M., Nikkel, S.M., Stade, B.C., Rasmussen, C., Munoz, D.P., and
480 Reynolds, J.N. 2009. Executive function deficits in children with fetal alcohol
481 spectrum disorders (FASD) measured using the Cambridge Neuropsychological
482 Tests Automated Battery (CANTAB). J Child Psychol Psychiatry. **50**(6): 688–
483 697.
484 Habbick, B.F., Nanson, J.L., Snyder, R.E., Casey, R.E., and Schulman, A.L. 1995. Foetal
485 alcohol syndrome in Saskatchewan: unchanged incidence in a 20-year period. Can
486 J Public Health. **87**(3): 204–207.
487 Hamilton, D.A., Barto, D., Rodriguez, C.I., Magcalas, C.M., Fink, B.C., Rice, J.P., et al.
488 2014. Effects of moderate prenatal alcohol exposure and age on social behavior,
489 spatial response perseveration errors and motor behavior. Behav Brain Res. **269**:
490 44–54.
491 Higgins, J.P., and Thompson, S.G. 2002. Quantifying heterogeneity in a meta-analysis.
492 Stat Med. **21**(11): 1539–1558.
493 Hoyme, H.E., Kalberg, W.O., Elliott, A.J., Blankenship, J., Buckley, D., Marais, A.S., et
494 al. 2016. Updated clinical guidelines for diagnosing fetal alcohol spectrum
495 disorders. Pediatrics. **138**(2): e20154256.
496 Jones, K.L., and Smith, D.W. 1973. Recognition of the fetal alcohol syndrome in early
497 infancy. Lancet, **302**(7836), 999–1001.

498 Kable, J.A., O'Connor, M.J., Olson, H.C., Paley, B., Mattson, S.N., Anderson, S.M., and
499 Riley, E.P. 2016. Neurobehavioral disorder associated with prenatal alcohol
500 exposure (ND-PAE): Proposed DSM-5 diagnosis. Child Psychiatry Hum Dev.
501 **47**(2): 335–346.
502 Kessler, R.C., Chiu W.T., Demler, O., and Walters, E.E. 2005. Prevalence, severity, and
503 comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey
504 Replication. Arch Gen Psychiatry. **62**(2): 617–627.
505 Kvigne, V.L., Leonardson, G.R., Neff-Smith, M., Brock, E., Borzelleca, J., and Welty,
506 T.K. 2004. Characteristics of children who have full or incomplete fetal alcohol
507 syndrome. J Pediatr. **145**(5), 635–640.
508 Landgraf, M.N., Nothacker, M., Heinen, F. 2013. Diagnosis of fetal alcohol syndrome
509 (FAS): German guideline version 2013. Eur J Paediatr Neurol. **17**(5): 437–446.
510 Landgren, M., Svensson, L., Strömland, K., and Grönlund, M.A. 2010. Prenatal alcohol
511 exposure and neurodevelopmental disorders in children adopted from eastern
512 Europe. Pediatrics. **125**(5), e1178–e1185.
513 Lewis, C.E., Thomas, K.G., Molteno, C.D., Kliegel, M., Meintjes, E.M., Jacobson, J.L.,
514 and Jacobson, S.W. 2016. Prospective Memory Impairment in Children with
515 Prenatal Alcohol Exposure. Alcohol Clin Exp Res. **40**(5), 969–978.
516 Mahan, S., and Matson, J.L. 2011. Children and adolescents with autism spectrum
517 disorders compared to typically developing controls on the Behavioral
518 Assessment System for Children, Second Edition (BASC-2). Res Autism Spectr
519 Disord. **5**(1): 119–125.

520 Matson, J.L., Wilkins, J., and Macken, J. 2009. The relationship of challenging behaviors
521 to severity and symptoms of autism spectrum disorders. J Ment Health Res
522 Intellect Disabil. **2**(1): 29–44.
523 Mattson, S.N., and Riley, E.P. 2000. Parent ratings of behavior in children with heavy
524 prenatal alcohol exposure and IQ-matched controls. Alcohol Clin Exp Res. **24**(2):
525 226–231.
526 McLennan, J.D. 2015. Misattributions and potential consequences: The case of child
527 mental health problems and fetal alcohol spectrum disorders. Can J Psychitry.
528 60(12): 587–590.
529 Mukherjee, R., Layton, M., Yacoub, E., and Turk, J. 2011. Autism and autistic traits in
530 people exposed to heavy prenatal alcohol: data from a clinical series of 21
531 individuals and nested case control study. Adv Ment Health Intellect
532 Disabil. **5**(1): 42–49.
533 Munn, Z., Moola, S., Riitano, D., and Lisy, K. 2014. The development of a critical
534 appraisal tool for use in systematic reviews addressing questions of prevalence.
535 Int J Health Policy Manag. **3**(3):123–128.
536 Nash, K., Rovet, J., Greenbaum, R., Fantus, E., Nulman, I., and Koren, G. 2006.
537 Identifying the behavioural phenotype in fetal alcohol spectrum disorder:
538 Sensitivity, specificity and screening potential. Arch Womens Ment Health. **9**(4):
539 181–186.
540 O'Connor, M.J., Shah, B., Whaley, S., Cronin, P., Gunderson, B., and Graham, J. 2002.
541 Psychiatric illness in a clinical sample of children with prenatal alcohol
542 exposure. Am J Drug Alcohol Abuse. **28**(4): 743–754.

543 Paintner, A., Williams, A.D., Burd, L. 2012. Fetal alcohol spectrum disorders–
544 Implications for child neurology, Part 2: Diagnosis and management. J Child
545 Neurol. **27**(3):355–362.
546 Payne, J., Elliott, E., D'Antoine, H., O'Leary, C., Mahony, A., Haan, E., and Bower, C.
547 2005. Health professionals' knowledge, practice and opinions about fetal alcohol
548 syndrome and alcohol consumption in pregnancy. Aust N Z J Public Health.
549 **29**(6): 558–564.
550 Popova, S., Lange, S., Burd, L., and Rehm, J. 2012. Health care burden and cost
551 associated with Fetal Alcohol Syndrome in Canada: based on official Canadian
552 data. PLoS One, **7**(8): e43024.
553 Popova, S., Lange, S., Probst, C., and Rehm, J. 2017. Prevalence of alcohol consumption
554 during pregnancy and Fetal Alcohol Spectrum Disorders among the general and
555 Aboriginal populations in Canada and the United States. Eur J Med Genet. **60**(1):
556 32-48.
557 Rasmussen, C., Benz, J., Pei, J., Andrew, G., Schuller, G., Abele-Webster, L., et al. 2010.
558 The impact of an ADHD co-morbidity on the diagnosis of FASD. Can J Clin
559 Pharmacol. **17**(1): e165–e176.
560 Rodriguez, A., Olsen, J., Kotimaa, A.J., Kaakinen, M., Moilanen, I., Henriksen, T.B., et
561 al. 2009. Is prenatal alcohol exposure related to inattention and hyperactivity
562 symptoms in children? Disentangling the effects of social adversity. J Child
563 Psychol Psychiatry. **50**(9): 1073–1083.

564 Rücker, G., Schwarzer, G., Carpenter, J., and Olkin, I. 2009. Why add anything to
565 nothing? The arcsine difference as a measure of treatment effect in meta-analysis
566 with zero cells. Stat Med. **28**(5): 721–738.
567 Stevens, S.A., Nash, K., Koren, G., and Rovet, J. 2013. Autism characteristics in children
568 with fetal alcohol spectrum disorders. Child Neuropsychol. **19**(6), 579–587.
569 Staroselsky, A., Fantus, E., Sussman, R., Sandor, P., Koren, G., and Nulman, I. 2009.
570 Both parental psychopathology and prenatal maternal alcohol dependency can
571 predict the behavioral phenotype in children. Pediatric Drugs. **11**(1):22–25.
572 Streissguth, A.P., Bookstein, F.L., Barr, H.M., Sampson P.D., O'Malley, K., and Young,
573 J.K. 2004. Risk factors for adverse life outcomes in fetal alcohol syndrome and
574 fetal alcohol effects. J Dev Behav Pediatr. **25**(4): 228–238.
575 Strömland, K., Ventura, L.O., Mirzaei, L., Fontes de Oliveira, K., Marcelino Bandim, J.,
576 Parente Ivo, A., and Brandt, C. 2015. Fetal alcohol spectrum disorders among
577 children in a Brazilian orphanage. Birth Defects Res A Clin Mol Teratol. **103**(3),
578 178–185.
579 Totsika, V., Hastings, R.P., Emerson, E., Lancaster, G.A., and Berridge, D.M. 2011. A
580 population-based investigation of behavioural and emotional problems and
581 maternal health. Associations with autism spectrum disorder and intellectual
582 disability. J Child Psychol Psychiatry. **52**(1), 91–99.
583 U.S. Census Bureau. 2016. Estimates of the Total Resident Population and Resident
584 Population Age 18 Years and Older for the United States, States, and Puerto Rico:
585 July 1, 2016 (SCPRC-EST2016-18+POP-RES). U.S. Census Bureau, Population
586 Division.

587 Watkins, R.E., Elliott, E.J., Wilkins, A., Mutch, R.C., Fitzpatrick, J.P., Payne, J.M., et al.
588 2013. Recommendations from a consensus development workshop on the
589 diagnosis of fetal alcohol spectrum disorders in Australia. BMC Pediatr. **13**: 156.
590 Williams, L., Jackson, C., Choe, N., Pelland, L., Scott, S.H., and Reynolds, J.N. 2014.
591 Sensory-Motor Deficits in Children with Fetal Alcohol Spectrum Disorder
592 Assessed Using a Robotic Virtual Reality Platform. Alcohol Clin Exp Res. **38**(1),
593 116–125.

Table 1. Study characteristics and prevalence of ADHD, ASD, CD, and ODD among children with FASD reported in the identified studies

Reference; Country	Year(s) of data collection	Population	Age range in years (mean)	Gender: % of males	Sample size; Diagnostic breakdown	Prevalence of ADHD n (%)	Prevalence of ASD n (%)	Prevalence of CD n (%)	Prevalence of ODD n (%)	Diagnostic criteria used for comorbid disorders	FASD Diagnostic criteria used	Method of ascertainment
Astley 2010; United States of America	1993-2005	General population	0-50 (9.0)	59.6	1270*; FASD = 59 FAS + 95 pFAS 394 SE/AE + 722 ND/AE	447 (57.3%)	-	42 (3.3%)	119 (9.4%)	n/a	4-digit diagnostic code (Astley & Clarren, 1999)	Passive: medical records
Bell et al. 2010; Canada	n/a	General population	2-49 (15.2)	59.8	425; FASD = 86 FAS/pFAS + 339 ARND	200 (47.1%)	8 (1.9%)	-	42 (9.9%)	n/a	Canadian diagnostic guidelines (Chudley et al., 2005)	Passive: medical records
Burd et al. 2003; United States of America	n/a	General population	0-56 (8.2)	58.9	303; FASD = 152 FAS + 151 pFAS	219 (72.3%)	-	-	53 (17.5%)	n/a	FAS Diagnostic Checklist (Burd & Martsolf, 1989)	Passive: registry
CDC 1995; United States of America	1981-92	Aboriginal population	0-31 (8.0)	58.3	60; 60 FAS	12 (20.0%)	-	-	-	n/a	Sokol & Clarren (1989)	Passive: medical records
Chasnoff et al. 2015; United States of America	n/a	Foster and adopted children/youth	4-18 (9.4)	63.8	156; FASD = 93 FAS + 1 pFAS + 61 ARND + 1 ARBD	88 (56.4%)	8 (5.1%)	-	4 (2.6%)	n/a	4-digit diagnostic code (Astley & Clarren,	Active: psychological assessment

Reference; Country	Year(s) of data collection	Population	Age range in years (mean)	Gender: % of males	Sample size; Diagnostic breakdown	Prevalence of ADHD n (%)	Prevalence of ASD n (%)	Prevalence of CD n (%)	Prevalence of ODD n (%)	Diagnostic criteria used for comorbid disorders	FASD Diagnostic criteria used	Method of ascertainment
											1999)	
Chen et al. 2012; United States of America	2007	General population	4-12 (7.5)	66.7	33; FASD = 5 FAS/pFAS + 21 ND/AE + 7 SE/AE	25 (75.8%)	-	-	-	n/a	4-digit diagnostic code (Astley & Clarren, 1999)	Passive: parental reports
Clark et al. 2004; Canada	2002	General population	17-43 (22.0)	41.9	62; FASD = 34 FAS/probable FAS + 28 FAE/probable FAE	40 (64.5%)	-	-	3 (4.8%)	n/a	n/a	Passive: survey (caregivers)
Elgen et al. 2007; Norway	1999-2004	General population	0-16 (7.8)	59.6	45; FASD = 25 FAS + 22 other-FASD	42 (93.3%)[b]	-	-	-	ICD-10	CDC diagnostic criteria (Bertrand et al., 2004)	Passive: survey (health professionals)
Elliot et al. 2008; Australia	2001-04	General population (including Aboriginals)	0-15 (3.3, median)	53.3	92; FASD = 25 FAS + 65 pFAS + 2 suspected FAS	11 (12.0%)	-	-	-	n/a	IOM criteria (Stratton et al., 1996)	Passive: survey (health professionals)
Fryer et al. 2006; United States of America	n/a	General population	8-15 (12.1)	53.8	39; n/a	37 (94.9%)	-	7 (17.9%)	15 (38.5%)	DSM-IV	n/a	Passive: interview (caregivers)
Green et al. 2009; Canada	n/a	General population	8-15 (10.7)	49.4	89; n/a	53 (59.6%)	2 (2.2%)	3 (3.4%)	19 (21.3%)	n/a	Canadian diagnostic guidelines (Chudley	Passive: medical records

Reference; Country	Year(s) of data collection	Population	Age range in years (mean)	Gender: % of males	Sample size; Diagnostic breakdown	Prevalence of ADHD n (%)	Prevalence of ASD n (%)	Prevalence of CD n (%)	Prevalence of ODD n (%)	Diagnostic criteria used for comorbid disorders	FASD Diagnostic criteria used	Method of ascertainment
											et al., 2005)	
Habbick et al. 1996; Canada	1992-94	General population (including Aboriginals)	0-28 (6.3)	52.7	207; n/a	68 (32.9%)	7 (3.4%)	-	10 (4.8%)	n/a	Guidelines by the Fetal Alcohol Study Group of the Research Society on Alcoholism (Rossett, 1980) & Sokol & Clarren (1989)	Active: psychological assessment
Kvigne et al. 2004; United States of America	1981-93	Aboriginal population	4-21	53.8	78; FASD = 43 FAS + 35 "incomplete" FAS	20 (25.6%)	-	10 (12.8%)	-	n/a	n/a	Passive: medical records
Landgren et al. 2010; Sweden	1998-2002	Adopted children (from Eastern Europe)	5-10	56.8	37; FASD = 21 FAS + 10 pFAS + 6 ARND	21 (56.8%)	2 (5.4%)	2 (5.4%)	15 (40.5%)	DSM-IV	Revised IOM criteria (Hoyme et al., 2005)	Active: psychological assessment
Lewis et al. 2016; South Africa	n/a	General population	(11.0)	55.2	29; 29 FAS/pFAS	9 (31.0%)	-	-	-	Case definition provided	Revised IOM criteria (Hoyme et al., 2005)	Active: psychological assessment

Reference; Country	Year(s) of data collection	Population	Age range in years (mean)	Gender: % of males	Sample size; Diagnostic breakdown	Prevalence of ADHD n (%)	Prevalence of ASD n (%)	Prevalence of CD n (%)	Prevalence of ODD n (%)	Diagnostic criteria used for comorbid disorders	FASD Diagnostic criteria used	Method of ascertainment
O'Connor et al. 2002; United States of America	n/a	General population	5-13 (8.3)	78.3	23; FASD = 2 FAS + 4 pFAS + 17 ARND	3 (13.0%)	1 (4.3%)	-	-	DSM-IV	4-digit diagnostic code (Astley & Clarren, 1999)	Active: psychological assessment
Rasmussen et al. 2010; Canada	2005-08	General population	4-17 (8.8)	53.8	52; FASD = 1 FAS + 6 pFAS + 13 ND/AE + 32 SE/AE	33 (63.5%)	-	-	-	n/a	4-digit diagnostic code (Astley & Clarren, 1999)	Active: psychological assessment
Stevens et al. 2012; Canada	n/a	General population	8-12 (10.3)	52.0	25; FASD = 5 pFAS + 20 ARND	16 (64.0%)	-	-	5 (20.0%)	n/a	Canadian diagnostic guidelines (Chudley et al., 2005)	Passive: medical records
Strömland et al. 2015; Brazil	n/a	Children residing in an orphanage	2-12 (6.2)	43.8	16; FASD = 3 FAS + 6 pFAS + 7 ARND	6 (37.5%)	-	-	1 (6.3%)	DSM-IV & ICD-10	Revised IOM criteria (Hoyme et al., 2005)	Active: psychological assessment
Williams et al. 2014; Canada	n/a	General population	5-18 (11.5)	61.3	31; n/a	22 (71.0%)	-	-	-	n/a	Canadian diagnostic guidelines (Chudley et al., 2005)	Passive: medical records

ADHD: Attention Deficit Hyperactivity Disorder; ARBD: Alcohol-Related Birth Defects; ARND: Alcohol-Related Neurodevelopmental Disorder; ASD: Autism Spectrum Disorder; CD: Conduct Disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; ICD-10: International Classification of Diseases and Related Health Problems, 10th Revision; ODD: Oppositional Defiant Disorder; pFAS: Partial Fetal Alcohol Syndrome; n/a: not available; ND/AE: Neurobehavioral Disorder, Alcohol Exposed; SE/AE: Static Encephaly, Alcohol Exposed

*The sample size for Astley (2010) was 780 for ADHD, 1271 for CD, and 1268 for ODD

603 **Table 2.** Pooled prevalence (results from meta-analysis) of ADHD, ASD, CD, and ODD

604 among children with FASD and results of the tests of heterogeneity and publication bias

Diagnosis	Number of included studies	Number of subjects	Pooled prevalence estimate	95% Confidence interval		I^2	P-value (regression test)
				Lower	Upper		
ADHD	20	2,582	52.9%	43.7%	62.0%	94.6%	0.000
ASD	6	1,029	2.6%	1.4%	4.1%	15.1%	0.025
CD	5	1,514	7.0%	2.5%	13.2%	80.8%	0.534
ODD	11	2,719	12.9%	8.4%	18.2%	89.0%	0.046

605 ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CD:

606 Conduct Disorder; ODD: Oppositional Defiant Disorder

607 **Table 3.** Sub-analyses of the pooled prevalence (results from meta-analysis) of ADHD,

608 CD, and ODD among children with FASD by population and method of ascertainment

609 and results of the tests of heterogeneity and publication bias

Diagnosis; Population; Method of ascertainment	Number of included studies	Number of subjects	Pooled prevalence estimate	95% Confidence interval		I^2	P-value (regression test)
				Lower	Upper		
ADHD							
Population							
General population	15	2,235	57.5%	46.8%	67.8%	95.2%	0.000
Aboriginal population	2	138	23.1%	16.4%	30.6%	-	-
Children in care	3	209	55.1%	47.9%	62.1%	2.1%	0.060
Method of ascertainment							
Active	7	520	42.1%	29.4%	55.4%	86.2%	0.007
Passive	13	2,062	58.5%	46.7%	69.8%	95.8%	0.005
CD							
Population							
General population	3	1,399	5.8%	1.2%	13.1%	81.3%	0.932
Method of ascertainment							
Passive	4	1,477	7.5%	2.3%	15.0%	85.3%	0.725
ODD							
Population							
General population	8	2,418	13.0%	8.6%	18.1%	87.2%	0.097
Children in care	3	209	13.0%	0.0%	45.2%	94.0%	0.648
Method of ascertainment							
Active	4	416	10.0%	1.2%	24.4%	91.2%	0.546
Passive	7	2,211	14.7%	9.8%	20.4%	86.5%	0.097

610 ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; ODD:

611 Oppositional Defiant Disorder

612 *Note.* Sub-analyses were conducted for those disorders where heterogeneity was found to

613 be present, and as such, ASD was not included.

614 **Figure Captions**

615

616 **Figure 1.** Schematic diagram depicting the search strategy employed

617

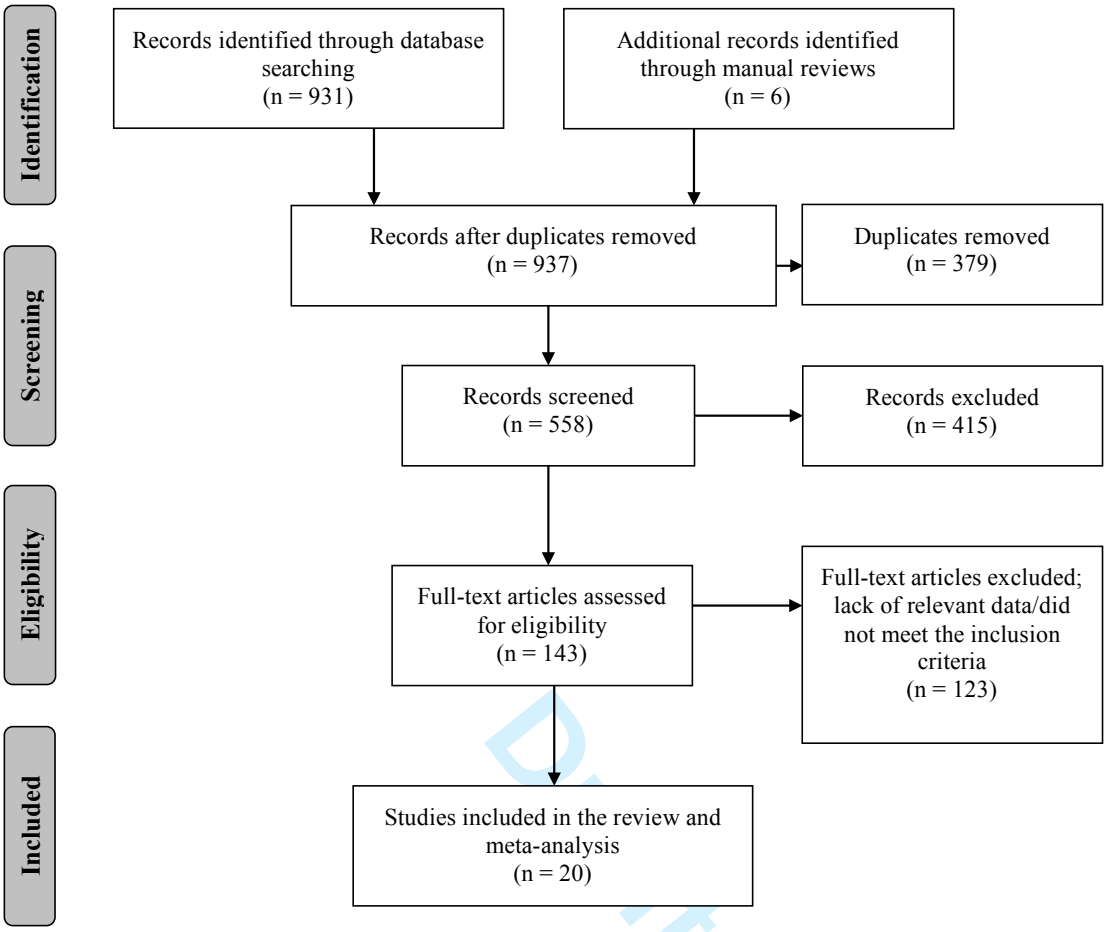
618 **Figure 2.** Forest plot of the prevalence of ADHD (A), ASD (B), CD (C), and ODD (D)
619 among children with FASD reported in the studies included in meta-analysis
620 CI: confidence interval.
621 *Note.* The size of the box around the point estimate is representative of the weight of the
622 estimate used in calculating the pooled point estimate.

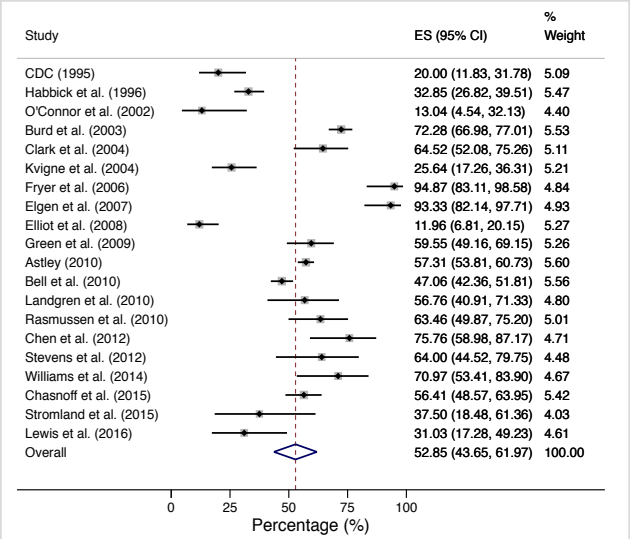
623

624 **Figure 3.** Funnel plot of the prevalence of ADHD (A), ASD (B), CD (C), and ODD (D)
625 among children with FASD reported in the studies included in meta-analysis

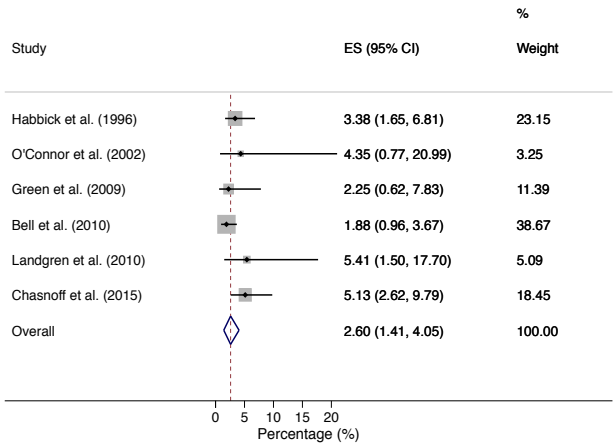
626

627 **Figure 4.** The prevalence of ADHD, ASD, CD and ODD among children with FASD and
628 without FASD (i.e., the general population of the United States)
629 ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CD:
630 Conduct Disorder; ODD: Oppositional Defiant Disorder
631 *Sources:* Christensen et al. (2016), Costello et al. (2003), and Kessler et al. (2005).

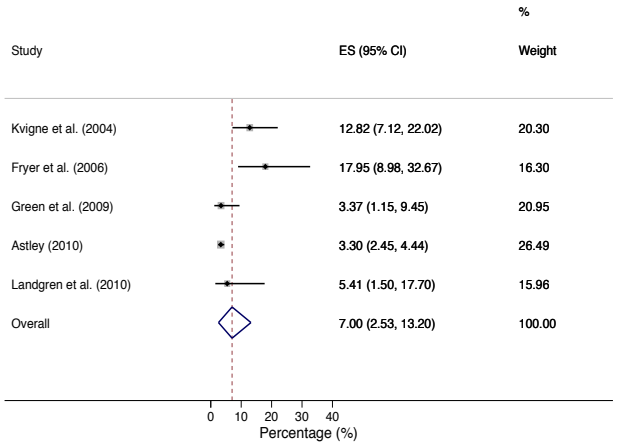

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 931)
Additional records identified through manual reviews (n = 6)
Records after duplicates removed (n = 937)
Duplicates removed (n = 379)
Records screened (n = 558)
Records excluded (n = 415)
Full-text articles assessed for eligibility (n = 143)
Full-text articles excluded; lack of relevant data/did not meet the inclusion criteria (n = 123)
Studies included in the review and meta-analysis (n = 20)


Study
ES (95% CI)
% Weight
CDC (1995) 20.00 (11.83, 31.78) 5.09
Habbick et al. (1996) 32.85 (26.82, 39.51) 5.47
O'Connor et al. (2002) 13.04 (4.54, 32.13) 4.40
Burd et al. (2003) 72.28 (66.98, 77.01) 5.53
Clark et al. (2004) 64.52 (52.08, 75.26) 5.11
Kvigne et al. (2004) 25.64 (17.26, 36.31) 5.21
Fryer et al. (2006) 94.87 (83.11, 98.58) 4.84
Elgen et al. (2007) 93.33 (82.14, 97.71) 4.93
Elliot et al. (2008) 11.96 (6.81, 20.15) 5.27
Green et al. (2009) 59.55 (49.16, 69.15) 5.26
Astley (2010) 57.31 (53.81, 60.73) 5.60
Bell et al. (2010) 47.06 (42.36, 51.81) 5.56
Landgren et al. (2010) 56.76 (40.91, 71.33) 4.80
Rasmussen et al. (2010) 63.46 (49.87, 75.20) 5.01
Chen et al. (2012) 75.76 (58.98, 87.17) 4.71
Stevens et al. (2012) 64.00 (44.52, 79.75) 4.48
Williams et al. (2014) 70.97 (53.41, 83.90) 4.67
Chasnoff et al. (2015) 56.41 (48.57, 63.95) 5.42
Stromland et al. (2015) 37.50 (18.48, 61.36) 4.03
Lewis et al. (2016) 31.03 (17.28, 49.23) 4.61
Overall 52.85 (43.65, 61.97) 100.00
0 25 50 75 100
Percentage (%)

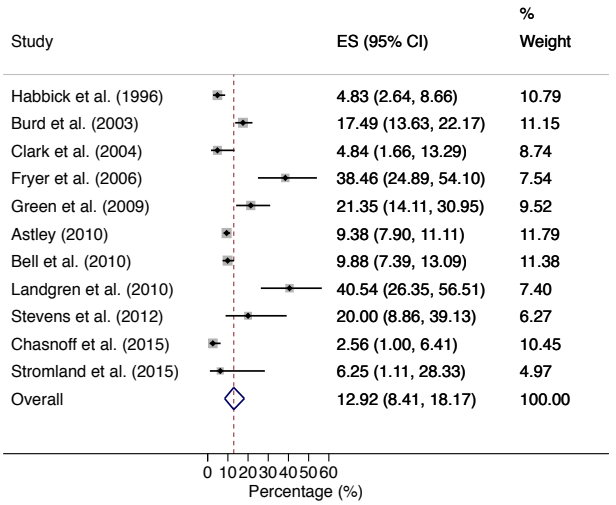
(A)


Study
ES (95% CI)
% Weight
Habbick et al. (1996) 3.38 (1.65, 6.81) 23.15
O'Connor et al. (2002) 4.35 (0.77, 20.99) 3.25
Green et al. (2009) 2.25 (0.62, 7.83) 11.39
Bell et al. (2010) 1.88 (0.96, 3.67) 38.67
Landgren et al. (2010) 5.41 (1.50, 17.70) 5.09
Chasnoff et al. (2015) 5.13 (2.62, 9.79) 18.45
Overall 2.60 (1.41, 4.05) 100.00
0 5 10 15 20
Percentage (%)

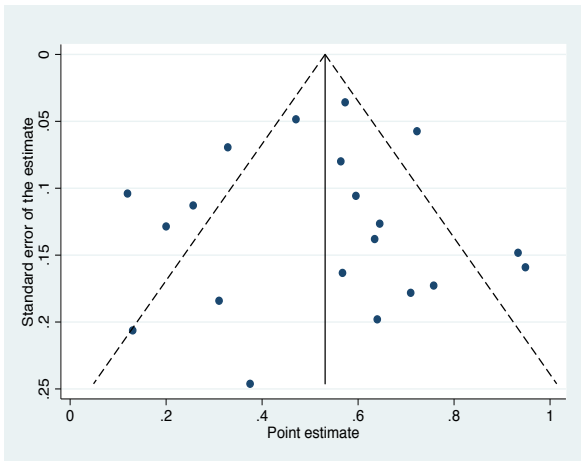
(B)


Study
ES (95% CI)
% Weight
Kvigne et al. (2004) 12.82 (7.12, 22.02) 20.30
Fryer et al. (2006) 17.95 (8.98, 32.67) 16.30
Green et al. (2009) 3.37 (1.15, 9.45) 20.95
Astley (2010) 3.30 (2.45, 4.44) 26.49
Landgren et al. (2010) 5.41 (1.50, 17.70) 15.96
Overall 7.00 (2.53, 13.20) 100.00
0 10 20 30 40
Percentage (%)

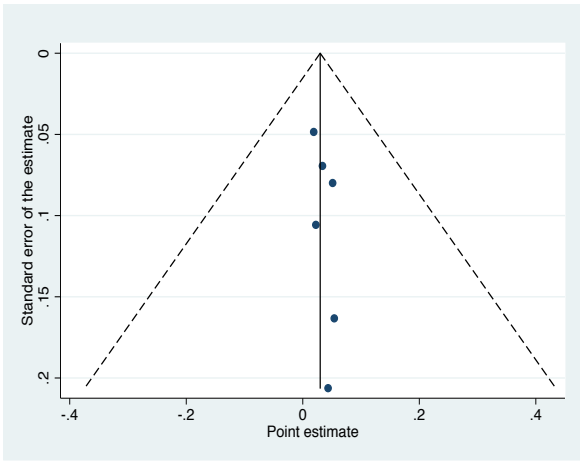
(C)


Study
ES (95% CI)
% Weight
Habbick et al. (1996) 4.83 (2.64, 8.66) 10.79
Burd et al. (2003) 17.49 (13.63, 22.17) 11.15
Clark et al. (2004) 4.84 (1.66, 13.29) 8.74
Fryer et al. (2006) 38.46 (24.89, 54.10) 7.54
Green et al. (2009) 21.35 (14.11, 30.95) 9.52
Astley (2010) 9.38 (7.90, 11.11) 11.79
Bell et al. (2010) 9.88 (7.39, 13.09) 11.38
Landgren et al. (2010) 40.54 (26.35, 56.51) 7.40
Stevens et al. (2012) 20.00 (8.86, 39.13) 6.27
Chasnoff et al. (2015) 2.56 (1.00, 6.41) 10.45
Stromland et al. (2015) 6.25 (1.11, 28.33) 4.97
Overall 12.92 (8.41, 18.17) 100.00
0 10 20 30 40 50 60
Percentage (%)

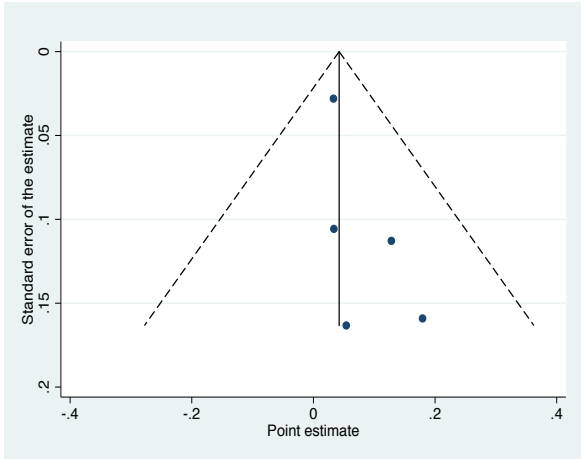
(D)


Standard error of the estimate
0
.05
.1
.15
.2
.25
0
.2
.4
.6
.8
1
Point estimate

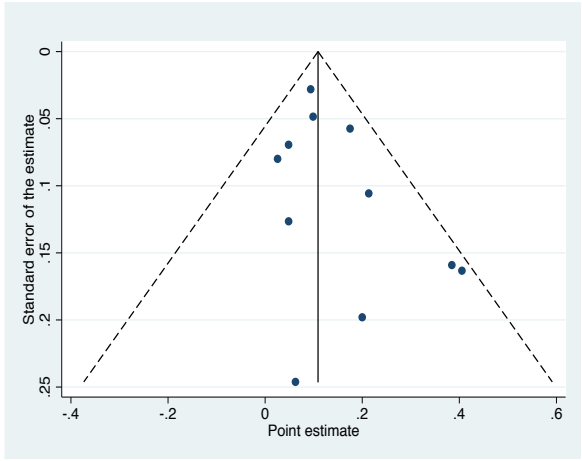
(A)


Standard error of the estimate
0
.05
.1
.15
.2
-.4
-.2
0
.2
.4
Point estimate

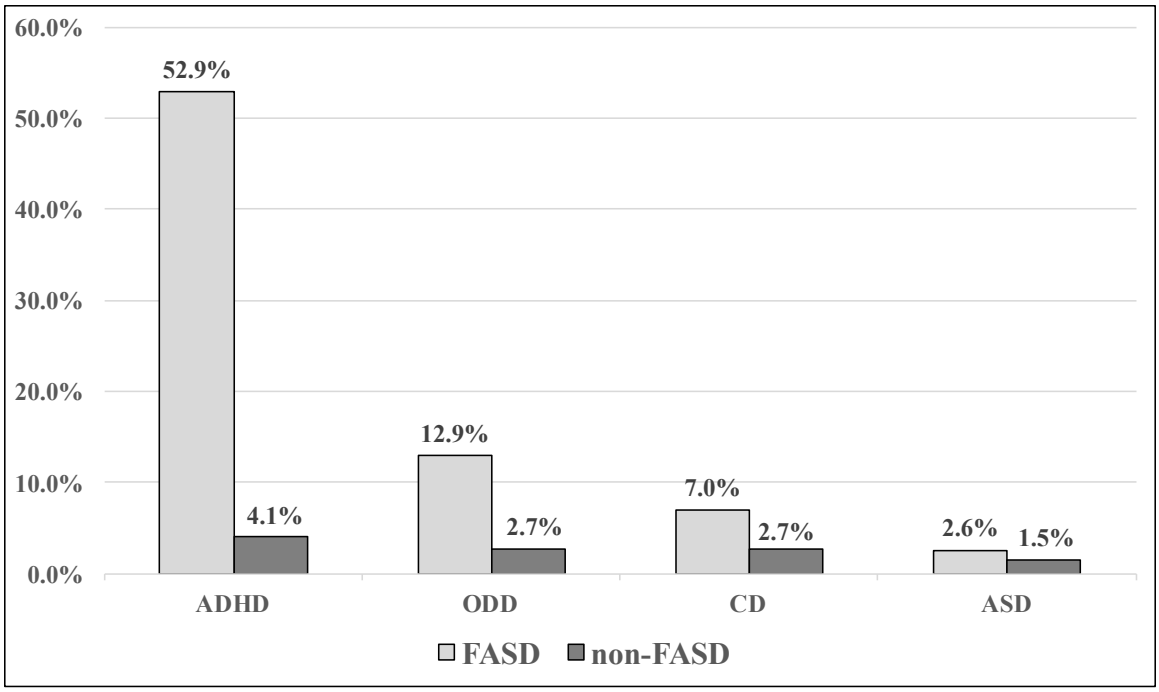
(B)


Standard error of the estimate
0
.05
.1
.15
.2
-.4
-.2
0
.2
.4
Point estimate

(C)


Standard error of the estimate
0
.05
.1
.15
.2
.25
-.4
-.2
0
.2
.4
.6
Point estimate

(D)


60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
52.9%
4.1%
12.9%
2.7%
7.0%
2.7%
2.6%
1.5%
ADHD
ODD
CD
ASD
FASD
non-FASD