Exploring the Existence of a Unique
Neurodevelopmental Profile of Fetal Alcohol Spectrum Disorder

by

Shannon Lange

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Shannon Lange
Doctor of Philosophy
Institute of Medical Science
University of Toronto
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Abstract

There is a general lack of consensus in the diagnostic criteria of Fetal Alcohol Spectrum Disorder (FASD), which has ultimately resulted in the overlapping of the diagnostic criteria with those of other neurodevelopmental disorders. As a result, FASD is associated with multiple potentially comorbid neurodevelopmental disorders, namely externalizing disorders. However, the extent to which FASD co-occurs with such disorders is largely unknown. Furthermore, the lack of universally accepted diagnostic criteria, and the high rate of comorbidity make diagnosing FASD difficult. Accordingly, in an effort to improve the diagnosis of FASD, researchers have explored the existence of a neurodevelopmental profile of FASD – defined as the outward expression (behavioral and developmental) of the central nervous system damage caused by prenatal alcohol exposure – however, a neurodevelopmental profile unique to FASD remains to be identified. Therefore, the objective of the current thesis project was to i) determine to what extent neurodevelopmental disorders with prominent externalizing behaviors co-occur among children with FASD; and ii) determine if children with FASD exhibit a unique and discernible
neurodevelopmental profile that will differentiate them from a) typically developing control children, and b) children with other neurodevelopmental disorders.

The first objective was achieved by way of a comprehensive systematic literature search, followed by disorder-specific random-effects meta-analyses. The second objective was achieved by performing latent profile analyses on two samples – i) children with FASD and typically developing control children, and ii) children with FASD, children with other neurodevelopmental disorders and typically developing control children – using data on neurodevelopmental status and behavior.

With respect to the prevalence of neurodevelopmental disorders with prominent externalizing behaviors among children with FASD, of the disorders investigated, Attention Deficit Hyperactivity Disorder was found to be the most common disorder, followed by Oppositional Defiant Disorder, Conduct Disorder and Autism Spectrum Disorder, in that order. In relation to the identification of a neurodevelopmental profile, the profile was successful in differentiating children with FASD from typically developing control children; however, it was unsuccessful in differentiating children with FASD from children with other neurodevelopmental disorders. These findings are reflective of the complexity of FASD and highlight the need for diagnostic refinement.
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Contributions

Shannon Lange – Conceptualization, planning, analysis and writing thesis.

Jürgen Rehm – Supervision and mentorship for entire thesis.

Svetlana Popova – Supervision and mentorship for entire thesis.

Joanne Rovet – Critical revisions of the paper on which the section on Existing neurodevelopmental profiles of FASD in Chapter 1 is modified.

Kevin Shield – Assistance in the statistical analysis of Chapters 4 and 5.
# Table of Contents

Abstract ................................................................................................................................. ii

Acknowledgements .............................................................................................................. iv

Contributions ........................................................................................................................ v

Table of Contents .................................................................................................................. vi

List of Tables .......................................................................................................................... x

List of Figures ........................................................................................................................ xii

List of Abbreviations .......................................................................................................... xiii

Chapter 1 Introduction to Fetal Alcohol Spectrum Disorder (FASD) ........................................ 1

1.1 Alcohol Use Among Women ............................................................................................ 2

1.1.1 Prevalence of alcohol use during pregnancy ............................................................... 2

1.1.2 Teratogenic effects of alcohol ...................................................................................... 6

1.1.2.1 Biological pathways and mechanisms of teratogenesis ......................................... 8

1.2 FASD ............................................................................................................................... 9

1.2.1 History of FASD ......................................................................................................... 10

1.2.2 Prevalence of FASD .................................................................................................... 10

1.2.2.1 General population ............................................................................................... 10

1.2.2.2 Special populations .............................................................................................. 13

1.2.3 Diagnosis of FASD .................................................................................................... 14

1.2.3.1 Canadian guidelines for FASD diagnosis ............................................................... 14

1.2.3.2 Recently proposed nomenclature .......................................................................... 18

1.2.3.3 Challenges of diagnosing FASD .......................................................................... 19

1.2.4 Neurodevelopmental impairments of FASD ............................................................... 22

1.2.4.1 Adaptive function ................................................................................................. 22

1.2.4.2 Attention .............................................................................................................. 23
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.4.3 Executive function</td>
<td>24</td>
</tr>
<tr>
<td>1.2.4.4 Intellectual ability</td>
<td>24</td>
</tr>
<tr>
<td>1.2.4.5 Language</td>
<td>25</td>
</tr>
<tr>
<td>1.2.4.6 Learning and memory</td>
<td>26</td>
</tr>
<tr>
<td>1.2.4.7 Motor function</td>
<td>26</td>
</tr>
<tr>
<td>1.2.4.8 Visual-spatial ability</td>
<td>27</td>
</tr>
<tr>
<td>1.2.5 Behavioral problems associated with FASD</td>
<td>28</td>
</tr>
<tr>
<td>1.2.6 Existing neurodevelopmental profiles of FASD</td>
<td>29</td>
</tr>
<tr>
<td>1.2.6.1 Neurodevelopmental profiles of FASD based on behavioral</td>
<td>29</td>
</tr>
<tr>
<td>observations/ratings by parents/caregivers</td>
<td>29</td>
</tr>
<tr>
<td>1.2.6.2 Neurodevelopmental profiles of FASD based on subtest scores</td>
<td>39</td>
</tr>
<tr>
<td>from a battery of standardized tests</td>
<td></td>
</tr>
<tr>
<td>1.2.6.3 Summary</td>
<td>45</td>
</tr>
<tr>
<td>Chapter 2 Aims and Hypotheses</td>
<td>52</td>
</tr>
<tr>
<td>2.1 Objective</td>
<td>53</td>
</tr>
<tr>
<td>2.2 Specific Aims and Hypotheses</td>
<td>53</td>
</tr>
<tr>
<td>2.2.1 Specific Aim I</td>
<td>53</td>
</tr>
<tr>
<td>2.2.2 Specific Aim II</td>
<td>54</td>
</tr>
<tr>
<td>2.2.3 Specific Aim III</td>
<td>54</td>
</tr>
<tr>
<td>Chapter 3 Prevalence of Externalizing Disorders and ASD Among Children with FASD</td>
<td>56</td>
</tr>
<tr>
<td>3.1 Background</td>
<td>57</td>
</tr>
<tr>
<td>3.2 Methods</td>
<td>59</td>
</tr>
<tr>
<td>3.2.1 Comprehensive systematic literature search</td>
<td>59</td>
</tr>
<tr>
<td>3.2.1.1 Inclusion and exclusion criteria</td>
<td>60</td>
</tr>
<tr>
<td>3.2.1.2 Data selection and extraction</td>
<td>60</td>
</tr>
<tr>
<td>3.2.1.3 Critical appraisal of existing studies</td>
<td>61</td>
</tr>
</tbody>
</table>
3.2.2 Meta-analysis ........................................................................................................ 61
3.2.3 Comparison of the prevalence of ADHD, ASD, CD and ODD among children with
FASD to the prevalence among those without FASD ................................................. 63
3.3 Results ..................................................................................................................... 63
3.3.1 Comprehensive systematic literature search ......................................................... 63
  3.3.1.1 Critical appraisal of existing studies ................................................................. 64
3.3.2 Meta-analysis ..................................................................................................... 66
  3.3.2.1 Pooled prevalence of ADHD, ASD, CD and ODD among children with FASD
................................................................................................................................. 66
3.3.3 Comparison of the prevalence of ADHD, ASD, CD and ODD among children with
FASD to the prevalence among those without FASD ................................................. 75
3.4 Discussion ............................................................................................................... 77
Chapter 4 Identification of a Neurodevelopmental Profile of FASD: FASD versus Typically
Developing Control Children ......................................................................................... 85
4.1 Introduction ............................................................................................................ 86
4.2 Methods ................................................................................................................ 87
  4.2.1 Participants ....................................................................................................... 87
4.2.2 Measures ......................................................................................................... 90
  4.2.2.1 Neurodevelopmental assessment ................................................................. 90
  4.2.2.2 Behavioral observations/ratings by parents ............................................... 91
4.2.3 Latent profile analysis ....................................................................................... 91
  4.2.3.1 Model selection ......................................................................................... 92
  4.2.3.2 Model evaluation ...................................................................................... 92
4.2.4 Post-hoc analysis ............................................................................................ 93
4.2.5 Missing data imputation .................................................................................. 93
4.2.6 Statistical software ......................................................................................... 94
4.3 Results.................................................................................................................................94
  4.3.1 Post-hoc analysis: Latent profile analysis based on IQ only .........................98
  4.3.2 Sensitivity analysis .....................................................................................................100
  4.4 Discussion .....................................................................................................................100

Chapter 5 Exploring the Uniqueness of the Identified Neurodevelopmental Profile of FASD
..................................................................................................................................................105
  5.1 Introduction ....................................................................................................................106
  5.2 Methods ........................................................................................................................107
    5.2.1 Participants ..............................................................................................................107
    5.2.2 Neurodevelopmental profile ..................................................................................108
    5.2.2 Statistical analysis .................................................................................................109
      5.2.2.1 Missing data imputation ..................................................................................110
      5.2.2.2 Latent profile analysis .....................................................................................110
      5.2.2.3 Sensitivity analysis ..........................................................................................111
      5.2.2.4 Statistical software ..........................................................................................112
    5.3 Results ........................................................................................................................112
      5.3.1 Sensitivity analysis ...............................................................................................124
    5.4 Discussion ....................................................................................................................127

Chapter 6 Discussion ..............................................................................................................133

Chapter 7 Conclusion and Future Directions .......................................................................143

References .............................................................................................................................147
List of Tables

Table 1. Canadian diagnostic criteria for FAS, pFAS and ARND ..................................................15
Table 2. Neurobehavioral Screening Tool (NST) ..........................................................31
Table 3. Classification accuracy of the Neurobehavioral Screening Tool reported in the individual studies ..........................................................................................................................34
Table 4. Measures included in the profile and neurodevelopmental domains assessed by Mattson and colleagues (2010) ..................................................................................................................41
Table 5. Measures included in the profile and neurodevelopmental domains assessed by Mattson and colleagues (2013) ..................................................................................................................47
Table 6. Measures included in the profile and neurodevelopmental domains assessed by Enns and Taylor (2018) ..................................................................................................................48
Table 7. Study characteristics and prevalence of ADHD, ASD, CD, and ODD among children with FASD reported in the identified studies ..........................................................67
Table 8. Pooled prevalence (results from meta-analysis) of ADHD, ASD, CD and ODD among children with FASD and results of the tests of heterogeneity and publication bias...75
Table 9. Sub-analyses of the pooled prevalence (results from meta-analysis) of ADHD, CD and ODD among children with FASD by population and method of ascertainment and results of the tests of heterogeneity and publication bias ..........................................................79
Table 10. Demographic and descriptive characteristics of study participants ..................95
Table 11. Model fit statistics for the 1-, 2-, and 3-class models tested ..................................97
Table 12. Mean scores for each subgroup in the 2-class model ........................................99
Table 13. Number of children assigned to each subgroup and the classification function of the 2-class model for the main and sensitivity analysis .................................................101
Table 14. Demographic and descriptive characteristics of study participants ..............114
Table 15. Model fit statistics for the 1-, 2-, 3-, 4-, and 5-class models tested ..................117
Table 16. Mean scores for each subgroup in the 2-class model ........................................... 118

Table 17. Number of children assigned to each subgroup in the 2- (main analysis) and 4-class (sensitivity analysis) models ................................................................. 121

Table 18. Classification function of the 2- (main analysis) and 4-class (sensitivity analysis) models ........................................................................................................... 122

Table 19. Mean scores for each subgroup in the 4-class model (sensitivity analysis) ....... 125

Table 20. Number of children assigned to each subgroup in the 4-class model (sensitivity analysis) ................................................................. 128

Table 21. Classification function of the 4-class model (sensitivity analysis) ................. 129
List of Figures

**Figure 1.** Global prevalence (%) of alcohol use (any amount) during pregnancy among the general population in 2012........................................................................................................................................4

**Figure 2.** Prevalence (%) of binge drinking (four or more drinks on a single occasion) during pregnancy among the general population by country in 2012 ................................................................................5

**Figure 3.** Global prevalence (per 1,000) of FASD among children and youth in the general population in 2012 .........................................................................................................................12

**Figure 4.** The 5-point lip-philtrum guide........................................................................................................................................19

**Figure 5.** Schematic diagram depicting the search strategy employed .........................................................................................65

**Figure 6.** Forest plot of the prevalence of ADHD (A), ASD (B), CD (C) and ODD (D) among children with FASD reported in the studies included in meta-analysis ........................................................................76

**Figure 7.** Funnel plot of the prevalence of ADHD (A), ASD (B), CD (C) and ODD (D) among children with FASD reported in the studies included in meta-analysis ................................................................78

**Figure 8.** The prevalence of ADHD, ASD, CD and ODD among children with FASD and without FASD (i.e., the general population of the United States) ...............................................................................81

**Figure 9.** Mean scores for each subgroup in the 2-class model (main analysis) .........................................................119

**Figure 10.** Mean scores for each subgroup in the 4-class model (sensitivity analysis) ........................................120

**Figure 11.** Mean scores on each of the latent variables included in the LPA for typically developing control children and children with ADHD only, ASD only and suspected FASD only ........................................................................................................................................130
List of Abbreviations

ADH: Alcohol Dehydrogenase
ADHD: Attention Deficit Hyperactivity Disorder
ANOVA: Analysis of variance
ARBD: Alcohol-Related Birth Defects
ARND: Alcohol-Related Neurodevelopmental Disorder
ASD: Autism Spectrum Disorder
BRIEF: Behavior Rating Inventory of Executive Function
CANTAB: Cambridge Neuropsychological Test Automated Battery
CBCL: Child Behavior Checklist
CD: Conduct Disorder
CI: Confidence Interval
CMS: Children’s Memory Scale
D-KEFS: Delis-Kaplan Executive Function System
FAS: Fetal Alcohol Syndrome
FASD: Fetal Alcohol Spectrum Disorder
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
IOM: Institute of Medicine
LPA: Latent profile analysis
MCAR: Missing completely at random
MVWM: Morris Virtual Water Maze
ND-PAE: Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure
NES3: Neurobehavioral Evaluation System 3
NPV: Negative predictive value
NST: Neurobehavioral Screening Tool

ODD: Oppositional Defiant Disorder

OR: Odds Ratio

pFAS: Partial Fetal Alcohol Syndrome

PPV: Positive predictive value

RDoC: Research Domain Criteria

WASI-II: Wechsler Abbreviated Scales of Intelligence, Second Edition

WHO: World Health Organization

WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition

WMS-IV: Wechsler Memory Scale, Fourth Edition

WRAT4: Wide Range Achievement Test, Fourth Edition
Chapter 1 Introduction to Fetal Alcohol Spectrum Disorder (FASD)

Part of this chapter was modified from the following:
1.1 Alcohol Use Among Women

Globally, women are more often abstainers than men, and when they do consume alcohol (also known as ethanol or ethyl alcohol), they drink less on average and engage less often in heavy episodic drinking (six or more standard drinks [10g of pure alcohol] on a single occasion at least monthly) (World Health Organization, 2014). However, this gender gap appears to be narrowing (Keyes, Grant, & Hasin, 2008). The 2012 Canadian Alcohol and Drug Use Monitoring Survey found that 82.7% of men and 74.4% of women aged 15 years and older consumed alcohol in the 12 months preceding the survey (Health Canada, 2012). Further, the rates of alcohol use decline with age for both men and women, with the highest rates being reported for those aged 21 to 44 years (Substance Abuse and Mental Health Services Administration, 2011) – an age range that significantly overlaps with the reproductive years of women (15-49 years of age). Although most women reduce or stop their alcohol use upon pregnancy recognition, many pregnant women unintentionally expose the fetus to alcohol before they are aware of their pregnancy (Ethen et al., 2009; Tough, Tofflemire, Clarke, & Newburn-Cook, 2006) and some even continue to drink throughout their pregnancy (Ethen et al., 2009).

1.1.1 Prevalence of alcohol use during pregnancy

Given that the pattern, amount and/or critical period of prenatal alcohol exposure necessary for structural and/or functional teratogenesis are unknown, current medical guidelines recommend that no alcohol should be consumed over the period of conception and throughout pregnancy (see for example, Carson et al., 2010). Despite this, it was recently estimated that globally 9.8% of women consume alcohol while pregnant and thus, a number of pregnancies are alcohol-exposed worldwide (Popova, Lange, Probst, Gmel, & Rehm,
Popova and colleagues (Popova et al., 2017) recently estimated that the five countries with the highest prevalence of alcohol use during pregnancy in the world were Russia (36.5%), United Kingdom (41.3%), Denmark (45.8%), Belarus (46.6%) and Ireland (60.4%). See Figure 1 for the prevalence of alcohol use during pregnancy among the general population in 2012 by country estimated by Popova and colleagues (Popova et al., 2017). Further, a study conducted on cohorts from Australia, Ireland, New Zealand and the United Kingdom not only found that alcohol use during pregnancy was highly prevalent (ranging from 20%-82% in Ireland, and 46% in Australia, New Zealand and the United Kingdom), but also found high levels of binge drinking during pregnancy (as high as 45% in Ireland) (O'Keeffe et al., 2015).

Lange and colleagues (Lange, Probst, Rehm, & Popova, 2017) recently reported that in 40% of the countries included in their investigation of a total 162 countries, over 25% of the women who consumed any alcohol during pregnancy binge drank (defined as four or more drinks on a single occasion) (Lange, Probst, Rehm, et al., 2017). These results indicate that a large portion of pregnancies that are alcohol exposed are being exposed to the most detrimental pattern of drinking – binge drinking – which has been directly linked to Fetal Alcohol Spectrum Disorder (FASD) (May et al., 2014; May et al., 2005). Further, in this study (Lange, Probst, Rehm, et al., 2017), the five countries with the highest estimated prevalence of binge drinking during pregnancy were Paraguay (13.9%), Moldova (10.6%), Ireland (10.5%), Lithuania (10.5%) and Czech Republic (9.4%). See Figure 2 for the prevalence of binge drinking during pregnancy among the general population by country in 2012 estimated by Lange and colleagues (Lange, Probst, Rehm, et al., 2017).
Figure 1. Global prevalence (%) of alcohol use (any amount) during pregnancy among the general population in 2012

Source: (Popova et al., 2017)
Figure 2. Prevalence (%) of binge drinking (four or more drinks on a single occasion) during pregnancy among the general population by country in 2012

Source: (Lange, Probst, Rehm, et al., 2017)
1.1.2 Teratogenic effects of alcohol

Alcohol is a teratogen (an agent or factor that can impair fetal development and cause embryonic malformations) and is associated with a number of adverse pregnancy outcomes such as stillbirth (Kesmodel, Wisborg, Olsen, Henriksen, & Secher, 2002), spontaneous abortion (Henriksen et al., 2004), premature birth (Albertsen, Andersen, Olsen, & Gronbaek, 2004; Kesmodel, Olsen, & Secher, 2000; Patra et al., 2011) and intrauterine growth retardation (Patra et al., 2011). Additionally, drinking during pregnancy can interfere with the normal developmental progression of the developing fetus and result in a child being born with FASD (Jones & Smith, 1973; Jones, Smith, Ulleland, & Streissguth, 1973; Riley et al., 2003). Animal model-based studies have shown that the brain is vulnerable to the teratogenic effects of alcohol at virtually every stage of its development, and that a wide range of brain regions are susceptible to alcohol (Sulik, 2014). The deficits that can result from prenatal alcohol exposure range from gross structural abnormalities, such as microcephaly, to subtler damage including cell death or degeneration in various brain regions (Sulik, 2014). Although there is no known pattern of consumption or lower limit of prenatal alcohol exposure that is safe, animal studies have also shown that high blood alcohol concentrations are the most detrimental to a developing fetus (Clarren, Astley, Gunderson, & Spellman, 1992; Goodlett & Eilers, 1997; Livy, Miller, Maier, & West, 2003), and that the risk for adverse outcomes follows a dose-response relationship (Jacobson & Jacobson, 1994; Jacobson & Jacobson, 1999; Qiang, Wang, & Elberger, 2002; Savage, Becher, de la Torre, & Sutherland, 2002; Sood et al., 2001). A high blood alcohol concentration is achieved by consuming a large amount of alcohol over a relatively short period of time – i.e., binge drinking, which, during pregnancy, is defined as four or more standard drinks on a single occasion.
Sulik (Sulik, 2005) has shown that the characteristic facial dysmorphology of Fetal Alcohol Syndrome (FAS) and Partial FAS (pFAS; the visibly identifiable forms of FASD) can be produced in a mouse model following exposure to high dosages of alcohol on the 7th-9th day of gestation, which corresponds to the 3rd-4th week of gestation in humans. Another study of mice found that specific facial dysmorphologies were predictive of unique patterns of abnormal brain volume and shape (Lipinski et al., 2012). As such, it can be predicted that if a woman consumes a large amount of alcohol during this critical period, significant harm may be caused to the developing fetal brain. Also, the effects of drinking during pregnancy are likely to be time-specific and thus, depend on the stage of the embryonic development at the time of exposure (Thomas, Wasserman, West, & Goodlett, 1996).

Due to delayed pregnancy recognition, the first trimester is also the time that a fetus may be unintentionally exposed to alcohol. Studies on nonhuman primate models have suggested that binge drinking during early pregnancy followed by later gestational abstinence may produce a similar amount of gross brain damage and cognitive deficits as binge drinking throughout pregnancy (Astley, Magnuso, Omnell, & Clarren, 1999; Clarren et al., 1992). Alarmingly, it has been shown that the majority of women do not change their drinking habits prior to pregnancy recognition (Skagerstrom, Alehagen, Haggstrom-Nordin, Arestedt, & Nilsen, 2013; Tough et al., 2006) and therefore, prenatal alcohol exposure may occur during this time.

In human studies an association between prenatal binge drinking and significant adverse behavioral outcomes such as learning and memory deficits, and psychiatric disorders and traits that may not manifest until a later age, has been reported (Barr et al., 2006; Sayal et al., 2014). In a recent meta-analysis, Flak and colleagues (Flak et al., 2014) found a significant detrimental association between binge drinking during pregnancy and child
cognition. Further, after controlling for a range of prenatal and postnatal factors, Sayal et al. (Sayal et al., 2009) found that binge drinking in the absence of moderate daily use of alcohol during pregnancy was independently associated with higher risks for childhood mental health problems, particularly hyperactivity and inattention.

1.1.2.1 Biological pathways and mechanisms of teratogenesis

The toxic effects of alcohol on fetal growth and development, as well as other physiological impacts, are well known. There are multiple biological pathways and mechanisms of teratogenesis, but the type and severity of alcohol-induced damage depend on both the exposure pattern and dosage, developmental timing of exposure, the mother and fetus’s ability to metabolize alcohol, maternal stress, nutrition, co-occurring exposure to other substances, along with other genetic and epi-genetic factors (Eberhart & Parnell, 2016; May & Gossage, 2011).

The major components of the alcohol-induced pathogenesis include excessive cell death, changes in the cell cycle and proliferation, cell migration, cell morphogenesis, gene expression, free radical damage and interference with cell signaling and signaling pathways (Green et al., 2007; Petrelli, Weinberg, & Hicks, 2018; Sulik, 2014). Results of in vivo and in vitro studies show that embryos exposed to alcohol display dose-dependent embryonic retardation of growth and differentiation with reductions in RNA, DNA and protein content (Brown, Goulding, & Fabro, 1979; Rawat, 1975). Alcohol can also cause a disruption in the proliferation of stem cell populations, leading to a reduction in the generation of new neurons and glial cells (Guerri, Saez, Portoles, & Renau-Piqueras, 1993). In addition, cell damage or cell death can occur due to the interaction of ethanol with metabolizing enzymes in neural tissue (Goodlett, Horn, & Zhou, 2005). Animal model-based studies have shown
that heavy alcohol exposure during the period of synaptogenesis (comparable to that of the third trimester in humans) can cause death of post-mitotic neurons in the hypothalamus, cerebral cortex, cerebellum and associated brain-stem structures (Goodlett et al., 2005). Another mechanism of alcohol damage is causing neuronal migration errors, which lead to a disruption of cell adhesion and interference with glial-guided migration or detachment of neurons from glial fibers (Miller, 1993). Furthermore, it has been shown that alcohol affects dendritic morphology, which alters electrical excitability and firing patterns of the cells (Lindsley, Shah, & Ruggiero, 2011). Studies examining alcohol’s effect have also shown gene expression changes. As such, microarray analyses revealed downregulation of ribosomal proteins and upregulation of glycolysis, the pentose phosphate, tight junction, focal adhesion and actin cytoskeleton regulation pathways in embryos (Green et al., 2007). It has also been suggested that the excessive generation of free radicals, which can cause oxidative stress with subsequent damage to cellular components, including membranes, DNA, proteins and even apoptosis (programmed cell death) plays a role (Chen & Sulik, 2000).

1.2 FASD

FASD is a term that encompasses a range of disorders, all of which involve prenatal alcohol exposure as the etiological cause and includes the following alcohol-related diagnoses: 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).
1.2.1 History of FASD

It was first recognized in France in 1968 by Lemoine and colleagues (Lemoine, Harouusseau, Borteyru, & Menuet, 1968) that alcohol can have negative effects on pregnancy, fetal and child outcomes. Five years later, Jones and colleagues (Jones & Smith, 1973; Jones et al., 1973) used the term FAS to describe a group of children born to alcoholic mothers, who had growth impairments, specific facial characteristics and damage to the central nervous system. Since this time, the nomenclature and diagnostic criteria have been redefined multiple times, as it has been recognized that individuals prenatally exposed to alcohol exhibit a wide range of impairments and defects. As such, the term FASD was coined in 1996 by the United States’ Institute of Medicine (IOM) (Stratton, Howe, & Battaglia, 1996) in an effort to capture the range of effects that can occur in individuals prenatally exposed to alcohol.

1.2.2 Prevalence of FASD

1.2.2.1 General population

Empirical studies on the prevalence of FASD around the world are scarce, with the majority of existing studies coming from some European countries, the United States and South Africa (Lange, Probst, Gmel, et al., 2017). In Croatia, Petković and Barišić (Petkovic & Barisic, 2010, 2013) have reported the prevalence of FASD to be 40.7-66.8 per 1,000. In France, the reported prevalence of FASD has been estimated to range from and 5.6-66.0 per 1,000 (Serreau et al., 2002; Toutain & Lejeune, 2008). The prevalence of FASD in Italy has been reported to be 40.5-47.1 per 1,000 (May et al., 2011; May et al., 2006). A recent study in four diverse communities in the Rocky Mountain, Midwestern, Southeastern and
Pacific Southwestern regions of the United States reported the prevalence of FASD to be between 1% to 5% (using a conservative approach to estimation) and 3% to 10% (using a less conservative approach) (May et al., 2018). These new estimates for the United States are up to ten times higher than those previously reported using a similar methodology – active case ascertainment – from two single-site studies (May et al., 2014; May et al., 2015). Although these United States prevalence rates are high, especially for a largely preventable disorder, the highest-known prevalence of FASD has been reported in South Africa – from 63.9 to 207.5 per 1,000 (May et al., 2013; Urban et al., 2015).

Recently, Lange and colleagues (Lange, Probst, Gmel, et al., 2017) conducted country-specific random effects meta-analyses for all countries with two or more empirical studies on the prevalence of FASD among the general population, and for countries with one or no empirical studies, the prevalence was predicted based on the proportion of women who consumed alcohol during pregnancy per one case of FASD. The results showed that the prevalence of FASD varies significantly between countries. The five countries with the highest prevalence of FASD were South Africa (111.1 per 1,000), Croatia (53.3 per 1,000), Ireland (47.5 per 1,000), Italy (45.0 per 1,000), and Belarus (36.6 per 1,000). These investigators estimated that the global prevalence of FASD among children and youth in the general population is 7.7 per 1,000 – this means that approximately eight out of 1,000 children and youth in the general population have FASD (Lange, Probst, Gmel, et al., 2017). See Figure 3 for the prevalence of FASD among children and youth in the general population in 2012 estimated by Lange and colleagues (Lange, Probst, Gmel, et al., 2017).
Figure 3. Global prevalence (per 1,000) of FASD among children and youth in the general population in 2012

Source: (Lange, Probst, Gmel, et al., 2017)
1.2.2.2 Special populations

When compared to the prevalence of FASD among the general population, the prevalence of FASD among special populations such as Aboriginal and correctional populations and children in care, has been found to be notably higher (Lange, Probst, Gmel, et al., 2017). With respect to Aboriginal populations, the prevalence of FASD has been reported for only three countries: in Australia, the reported prevalence of FASD ranges from 4.1 per 1,000 (Mutch, Watkins, & Bower, 2015) to 194.4 per 1,000 (Fitzpatrick et al., 2017); in Canada, the reported prevalence of FASD ranges from 7.0 per 1,000 (Werk, Cui, & Tough, 2013) to 189.7 per 1,000 (Robinson, Conry, & Conry, 1987); and in the United States, the reported prevalence of FASD ranges from 0.4 per 1,000 (National Birth Defects Prevention Network, 2003) to 9.3 per 1,000 (Quaid, Kirkpatrick, Nakamura, & Aase, 1993). Further, in Australia, the prevalence of FASD among a correctional population was reported to be 363.6 per 1,000 (Bower et al., 2018); and in Canada, the reported prevalence of FASD ranges from 17.5 per 1,000 (McLachlan, 2017) to 233.5 per 1,000 (Fast, Conry, & Loock, 1999).

Children in care constitute another high-risk population with regard to the prevalence of FASD, as indicated by the reported prevalence rates among children residing in a Brazilian orphanage (170.2 per 1,000) (Stromland et al., 2015), children in orphanages in Lithuania (397.6 per 1,000) (Kuzmenkovičienė, Prasauskienė, & Endzinienė, 2012), Swedish adoptees from Eastern Europe (521.1 per 1,000) (Landgren, Svensson, Stromland, & Andersson Gronlund, 2010), and Russian children adopted by families in the United States (344.8 per 1,000) (Farina, Leifer, & Chasnoff, 2004).
1.2.3 Diagnosis of FASD

In 1996, the IOM defined five diagnostic categories of FASD: FAS with and without confirmed alcohol exposure, pFAS, ARND and ARBD (Stratton et al., 1996). However, the IOM guidelines were considered vague and did not adequately define the diagnostic criteria for each category, nor were there any guidelines for assessment (Hoyme et al., 2005; Manning & Eugene Hoyme, 2007). Since this time, major advancements have been made with respect to resolving the ambiguity of previous diagnostic categories and their respective criteria (Astley, 2004; Chudley et al., 2005; Hoyme et al., 2016; Hoyme et al., 2005).

1.2.3.1 Canadian guidelines for FASD diagnosis

In 2005, the Canadian FASD diagnostic guidelines were published by a subcommittee of the Public Health Agency of Canada’s National Advisory Committee on FASD (Chudley et al., 2005). The guidelines were based on widespread consultation among Canadian and American experts in the diagnosis of FASD and its related disabilities and recommend a multidisciplinary approach to diagnosis. The guidelines suggest that the core multidisciplinary team consist of the following professionals with appropriate qualifications, training and experience in their particular discipline: coordinator for case management, physician with specific training in FASD diagnosis, psychologist, occupational therapist, and speech-language pathologist.

According to the Canadian FASD Diagnostic Guidelines (Chudley et al., 2005), FASD includes the following three diagnoses: FAS, pFAS and ARND. These guidelines specify that the term ARBD should not be used as a diagnostic term for the spectrum of alcohol-related birth defects, rather ARBD constitutes a list of congenital anomalies, including
malformations and dysplasias and should be used with caution. See Table 1 for the diagnostic criteria of the 2005 Canadian guidelines for FASD diagnosis.

Table 1. Canadian diagnostic criteria for FAS, pFAS and ARND

1. The criteria for the diagnosis of FAS, after excluding other diagnoses, are:

   A. Evidence of prenatal or postnatal growth impairment, as in at least 1 of the following:
      a. Birth weight or birth length at or below the 10th percentile for gestational age.
      b. Height or weight at or below the 10th percentile for age.
      c. Disproportionately low weight-to-height ratio (= 10th percentile).

   B. Simultaneous presentation of all 3 of the following facial anomalies at any age:
      a. Short palpebral fissure length (2 or more standard deviations below the mean).
      b. Smooth or flattened philtrum (rank 4 or 5 on the lip-philtrum guide).
      c. Thin upper lip (rank 4 or 5 on the lip-philtrum guide).

   C. Evidence of impairment in 3 or more of the following central nervous system domains: hard and soft neurologic signs; brain structure; cognition; communication; academic achievement; memory; executive functioning and abstract reasoning; attention deficit/hyperactivity adaptive behavior, social skills, social communication.

   D. Confirmed (or unconfirmed) maternal alcohol exposure.

2. The diagnostic criteria for pFAS, after excluding other diagnoses, are:

   A. Simultaneous presentation of two of the following facial anomalies at any age:
      a. Short palpebral fissure length (2 or more standard deviations below the mean).
      b. Smooth or flattened philtrum (rank 4 or 5 on the lip-philtrum guide).
c. Thin upper lip (rank 4 or 5 on the lip-philtrum guide).

B. Evidence of impairment in three or more of the following central nervous system domains: hard and soft neurologic signs; brain structure; cognition; communication; academic achievement; memory; executive functioning and abstract reasoning; attention deficit/hyperactivity; adaptive behavior, social skills, social communication.

C. Confirmed maternal alcohol exposure.

3. The diagnostic criteria for ARND, after excluding other diagnoses, are:

A. Evidence of impairment in three or more of the following central nervous system domains: hard and soft neurologic signs; brain structure; cognition; communication; academic achievement; memory; executive functioning and abstract reasoning; attention deficit/hyperactivity; adaptive behavior, social skills, social communication.

B. Confirmed maternal alcohol exposure.

ARND: alcohol-related neurodevelopmental disorder; FAS: fetal alcohol syndrome; pFAS: partial fetal alcohol syndrome

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As specified in Table 1, there are three characteristic facial features that discriminate individuals with and without FAS or pFAS, which are:
1. Short palpebral fissures (the elliptic space between the medial and lateral canthi of the upper and lower lids), at or below the 3rd percentile (2 standard deviations below the mean);

2. Smooth or flattened philtrum (medial cleft; the “groove” above the upper lip), 4 or 5 on the 5-point Likert scale of the lip-philtrum guide (Figure 4) (Astley & Clarren, 2000)

3. Thin vermilion border (the red margin) of the upper lip, 4 or 5 on the 5-point Likert scale of the lip-philtrum guide (Figure 4) (Astley & Clarren, 2000).

The Canadian guidelines recommend that the following neurodevelopmental domains be evaluated during an FASD diagnostic assessment:

1. Hard and soft neurologic signs (including sensory-motor signs)
2. Brain structure (occipitofrontal circumference, magnetic resonance imaging, etc.)
3. Cognition (IQ)
4. Communication: receptive and expressive
5. Academic achievement
6. Memory
7. Executive functioning and abstract reasoning
8. Attention deficit/hyperactivity
9. Adaptive behavior, social skills, social communication

As per these guidelines, a domain is considered “impaired”: when on a standardized measure:

1. Scores are 2 standard deviations or more below the mean, or
2. There is a discrepancy of at least 1 standard deviation between subdomains. For example:
   i. Verbal versus non-verbal ability of standard IQ tests,
   ii. Expressive versus receptive language,
   iii. Verbal versus visual memory, or

3. There is a discrepancy of at least 1.5-2 standard deviations among subtests on a measure, taking into account the reliability of the specific measure and normal variability in the population.

Evidence of impairment in three domains is necessary for a diagnosis.

1.2.3.2 Recently proposed nomenclature

Recently, it has been proposed that FASD be used as a diagnostic term with the specification of the presence or absence of the sentinel facial features, rather than simply a non-diagnostic umbrella term (Cook et al., 2016). This is in line with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) where Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) was included as a condition that warrants further research and also as one specifier for the broader diagnostic term of Other Specified Neurodevelopmental Disorder. ND-PAE is intended to encompass the behavioral, developmental and mental health symptoms associated with prenatal alcohol exposure and is appropriate for individuals with or without physical findings (Kable et al., 2016).
1.2.3.3 Challenges of diagnosing FASD

Identifying a child exposed to alcohol prenatally is critical, as it can lead to early diagnosis, if appropriate, and if necessary, the implementation of timely interventions, which are key to...
improving the life of individuals with FASD. Further, early diagnosis has the potential to prevent subsequent alcohol-exposed births by providing appropriate interventions, treatment and support to the birth mothers (Astley, Bailey, Talbot, & Clarren, 2000). However, diagnosing FASD is challenging, as determining whether the affected individual's developmental deficits and behavioral problems are due to brain damage caused by prenatal alcohol exposure rather than other causes is a difficult undertaking. The challenges of diagnosing FASD are exacerbated by a number of factors, namely the high rate of comorbidity among individuals with FASD, a lack of uniformly accepted diagnostic criteria, and diagnostic criteria that overlap with other neurodevelopmental disorders. Recently, Popova and colleagues (Popova et al., 2016) revealed over 400 disease conditions associated with FASD, with the most prevalent conditions occurring within the Congenital malformations, deformities and chromosomal abnormalities (43%) and Mental and behavioral disorders (18%) chapters of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (World Health Organization, 2016). Some of these comorbid conditions (for example, language, auditory, visual, developmental/cognitive, mental and behavioral problems) were found to be highly prevalent among individuals with FAS, ranging from 50% to 91%, far exceeding the rates among the general population (Popova et al., 2016). It is reasonable to suspect that the large number of comorbid conditions can overshadow the core disorder – FASD – and ultimately lead to its underdiagnosis by way of misdiagnosis.

Further, there are currently a number of clinical guidelines for diagnosing FASD (Astley, 2004; Chudley et al., 2005; Cook et al., 2016; Hoyme et al., 2016; Landgraf, Nothacker, & Heinen, 2013; Watkins et al., 2013), and although there is considerable overlap in the criteria, the specific domains of function to be evaluated during the neurodevelopmental assessment are relatively undefined and lack consensus (Bastons-Compta, 2016).
diagnostic guidelines have had a tendency to focus on the severity of the neurodevelopmental impairments rather than the specificity of the impairments. This weakness of the former diagnostic guidelines mainly impacted the diagnosis of ARND, given that diagnosis is based primarily on the neurodevelopmental impairments the child exhibits as the characteristic facial traits and growth deficits associated with FAS and pFAS are often absent with ARND. Yet, ARND is recognized to be the largest category of affected individuals, representing as many as 80–90% of FASD cases (Chudley, 2008). In addition to the ambiguity surrounding the diagnosis of FASD, the neurodevelopmental assessment is thought to be the lengthiest and most cumbersome component of the diagnostic evaluation (Popova et al., 2013).

Moreover, the signs and symptoms common among individuals with FASD overlap with other neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) (McLennan, 2015). The general lack of consensus in the operationalization of the diagnostic criteria of FASD has resulted in the overlapping of the FASD diagnostic criteria with those of other neurodevelopmental disorders for which prenatal alcohol exposure is not etiologic (McLennan, 2015). As a result, individuals with FASD often receive multiple diagnoses before actually being assessed for and diagnosed with FASD (Chasnoff, Wells, & King, 2015).

In summary, FASD is often misdiagnosed (Chasnoff et al., 2015). Diagnostic misclassification can have a number of untoward consequences, particularly inappropriate treatments and interventions, mismanagement of behavioral symptoms, inaccurate incidence and prevalence estimates, and reduced ability to detect a significant difference between diagnostic groups in clinical research studies (Astley & Clarren, 2000; Chasnoff et
1.2.4 Neurodevelopmental impairments of FASD

As a teratogen, alcohol causes alterations to the developing brain and as a result, neurodevelopmental impairments. Thus, prenatal exposure to alcohol is associated with cognitive impairment in a number of neurodevelopmental domains. With the exception of ARBD, all of the disorders within the spectrum are associated with a broad array of neurodevelopmental deficits (Aragon et al., 2008; Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995; Nash et al., 2013). Specifically, individuals with FASD exhibit relative impairments in adaptive function, attention, executive function, intellectual ability, language, learning and memory, visual-spatial ability and motor function (Kodituwakku, 2009; Mattson, Crocker, & Nguyen, 2011). As such, a diagnosis of FASD can only be established following a thorough assessment of neurodevelopmental functioning.

1.2.4.1 Adaptive function

Adaptive function refers to the skills that are necessary for a person to navigate through the common demands of everyday life such as the ability to communicate with others and taking care of one’s own health. Children with FASD have been shown to have deficits across all domains of adaptive functioning (Crocker, Vaurio, Riley, & Mattson, 2009). Jirikowic and colleagues (Jirikowic, Kartin, & Olson, 2008) compared children with FASD to same aged typically developing children and found clear differences with regard to their adaptive skills, with children with FASD being rated significantly lower on the Scales of Independent Behavior-Revised in social interaction and communication, personal-living skills, and community-living skills and significantly higher on maladaptive behavior scales. Fagerlund
and colleagues (Fagerlund et al., 2012) found that children with FASD performed worse than IQ-matched children with specific learning disorder, who in turn performed worse than typically developing control children on all domains (communication, daily living skills and socialization) on the Vineland Adaptive Behaviour Scales. Further, evidence suggests that the adaptive functioning impairments of children with FASD fail to improve as they get older and thus, this suggests an arrest in development rather than a delay (Crocker et al., 2009; Whaley, O'Connor, & Gunderson, 2001).

1.2.4.2 Attention

Problems with attention are commonly observed in individuals prenatally exposed to alcohol (Bhatara, Loudenberg, & Ellis, 2006; Mattson & Riley, 1998), with affected children showing deficits in attention on neuropsychological tasks of vigilance, reaction time, and information processing (Burden, Jacobson, & Jacobson, 2005; Streissguth, Bookstein, Sampson, & Barr, 1995). It is also common for parents to report that their children with FASD have difficulty concentrating and cannot pay attention for long (Nash et al., 2006). Further, ADHD is the most common psychiatric comorbidity (Fryer, McGee, Matt, Riley, & Mattson, 2007), with as many as 72% of children with FASD having a comorbid diagnosis of ADHD (Burd, Klug, Martsoff, & Kerbeshian, 2003). However, when comparing children with FASD to children with ADHD, it has been reported that there are clear distinctions with respect to performance on behavioral and neurocognitive measures between the two clinical groups, with those with ADHD performing more poorly on conventional tests sensitive to attentional problems and conduct disorder than those with FASD (Coles et al., 1997).
1.2.4.3 Executive function

Executive function is a set of higher-order cognitive processes that enable us to plan, organize, problem solve, remember instructions and juggle multiple tasks at once. Rasmussen and colleagues (Rasmussen, Horne, & Witol, 2006) found that children with FASD displayed profound deficits on all scales of the Behavior Rating Inventory of Executive Function (BRIEF) – a validated multidimensional measure of executive function – with 79% of children having clinically significant scores on the Initiate scale (measures the ability to start a task and independently generate ideas, responses, or problem solving strategies), 72% having significant scores on the Shift scale (measures the ability to move freely from one task or situation to another) and 75% having significant scores on the Inhibit scale (measures inhibitory control and the ability to control one’s behavior). Another study found that executive function deficits (as per the two BRIEF summary indices) were predictive of poorer social skills and greater problem behaviors (Schonfeld, Paley, Frankel, & O’Connor, 2006). Further, Green et al. (2009) reported that children with FASD experience deficits in multiple executive function domains, including set shifting, planning and strategy use, attention and spatial working memory, and that these deficits did not differ between dysmorphic and non-dysmorphic individuals with FASD.

1.2.4.4 Intellectual ability

Although diminished intellectual functioning in children with FASD has been well-documented (Mattson, Riley, Gramling, Delis, & Jones, 1997), it is apparent that a wide range of individual variability exists among children with FASD exists (Mattson & Riley, 1998). Compared to children prenatally exposed to alcohol, but who did not have the characteristic dysmorphism necessary for a diagnosis of FAS, children with FAS tend to
be more severely impaired with respect to intellectual functioning (Mattson et al., 1997). This is in line with previous findings that a significant inverse relationship between growth deficiency/dysmorphic features and general cognitive function exists in children with FASD (Ervalahti et al., 2007). Further, a study by Chasnoff and colleagues (Chasnoff, Wells, Telford, Schmidt, & Messer, 2010) found that children with FAS have mean IQ scores significantly lower than children with pFAS/ARND, and that children with pFAS and ARND do not differ significantly from one another.

1.2.4.5 Language

Several studies have reported a high prevalence of speech-language disorders among individuals with FASD (Church et al., 1997; Egeland et al., 1998; Elliott, Payne, Morris, Haan, & Bower, 2008; Kvigne et al., 2004), with up to 60% of children with FAS having a speech-language disorder (Elliott et al., 2008). Prenatal alcohol exposure can disrupt an individual’s development and use of language (Mattson & Riley, 1998). Significant speech and language delays have been reported among individuals with FASD, with children with FASD exhibiting impairments in articulation, naming ability, word comprehension, and both receptive and expressive language abilities (Mattson & Riley, 1998). Neuroimaging research in children with FASD has also reported increased activation in left dorsal prefrontal regions and decreased activation in left medial and posterior temporal regions (as measured by functional magnetic resonance imaging) when compared to healthy controls while performing a verbal learning task (Sowell et al., 2007). Given that these regions have been shown to be involved in language processing (Saykin et al., 1999), these results are in agreement with behavioral findings of deficits in verbal learning (Willford, Richardson, Leech, & Day, 2004). In addition to poor receptive and expressive language skills, individuals with FASD often suffer from phonological deficits, fluency and articulation
difficulties and associated neurocognitive abnormalities that can adversely impact speech-language development (Church, Eldis, Blakley, & Bawle, 1997).

1.2.4.6 Learning and memory

Studies have shown that children prenatally exposed to alcohol present with deficits in both learning and recall of verbal information (Mattson & Roebuck, 2002), which has been demonstrated through difficulties with learning new words and recalling them freely or via recognition recall (Crocker, Vaurio, Riley, & Mattson, 2011; Mattson, Riley, Delis, Stem, & Jones, 1996). However, when the number of words are controlled for, prenatally alcohol exposed children show retention rates similar to those of typically developing control children (Kaemingk, Mulvaney, & Halverson, 2003; Willoughby, Sheard, Nash, & Rovet, 2008). Impairments of both types of visual memory – spatial and object – as well as both immediate and delayed recall have also been reported (Pei, Rinaldi, Rasmussen, Massey, & Massey, 2008). In short, the learning and memory impairments of children with FASD appear to span across both verbal and nonverbal domains (Richardson, Ryan, Willford, Day, & Goldschmidt, 2002).

1.2.4.7 Motor function

It has been reported that approximately 10% of children with FASD have poor motor function (Lucas et al., 2016) with impairments of both fine (involving the hands) and gross (involving the whole body) motor skills (Doney et al., 2014; Lucas et al., 2014). Findings of motor impairment in children with FASD include delayed motor reaction time (Simmons, Levy, Riley, Madra, & Mattson, 2009; Simmons, Thomas, Levy, & Riley, 2006), impaired fine-motor speed and coordination (Jirikovic, Olson, & Kartin, 2008) as well as poor visual-
motor integration (Doney et al., 2014) and hand-eye coordination (Adnams et al., 2001). However, it has been postulated that the structural defects observed in FASD such as skeletal malformations of the hands and feet (for example, camptodactyly) (Church et al., 1997), delayed skeletal maturity (Naidoo, Norval, Swanevelder, & Lombard, 2006) and atypical muscle development (David & Subramaniam, 2005) may interfere with motor abilities.

1.2.4.8 Visual-spatial ability

Difficulties with visual-spatial skills, including perception of visual information, understanding spatial relationships, spatial processing and spatial memory have been reported in children with FASD (Coles, Platzman, Lynch, & Freides, 2002; Crocker, Riley, & Mattson, 2015; Kaemingk & Halverson, 2000; Manji, Pei, Loomes, & Rasmussen, 2009). Olson and colleagues (Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998) found that not only were impairments in visual-spatial skills common among adolescents with FAS, but adolescents with FAS also performed more poorly on tasks measuring perceptions of spatial information and spatial memory than IQ-matched controls. Further, impaired mathematical ability, which relies heavily on visual-spatial skills, is common among individuals prenatally exposed alcohol, with or without FASD (Howell, Lynch, Platzman, Smith, & Coles, 2006; Rasmussen & Bisanz, 2009). The relationship between prenatal alcohol exposure and mathematics has been shown to follow a linear dose-response relationship, without any threshold affect (Goldschmidt, Richardson, Stoffer, Geva, & Day, 1996).
1.2.5 Behavioral problems associated with FASD

It is widely recognized that individuals with FASD commonly exhibit behaviors that are considered atypical (e.g., poor social skills, impulsivity and hyperactivity; Greenbaum, Stevens, Nash, Koren, & Rovet, 2009; Nash et al., 2006) and have increased rates of psychiatric disorders (Burd et al., 2003). In a well-known study on the adverse life outcomes of individuals with FASD, Streissguth and colleagues (2004) found that 61% had disrupted school experiences (suspended, expelled or dropped out), 60% trouble with the law (involvement with police, charged or convicted of crime), 50% confinement (inpatient treatment for mental health, alcohol/drug problems or incarceration for crime), 49% inappropriate sexual behaviors, and 35% alcohol and drug problems. These findings highlight that individuals with FASD have a range of behavioral outcomes that have a negative impact on their developmental trajectory. Furthermore, these investigators found that the most frequently reported behavior problems of children and youth with FASD in school were repeatedly having difficulty getting along with peers (58%) and being disruptive (55%). More recently, in a study utilizing data for 170 children who underwent an FASD diagnostic assessment it was found that children who received an FASD diagnosis were twice as likely to have Internalizing Problems scores (odds ratio [OR] = 2.5, 95% confidence interval [CI]: 1.2-5.3), four times more likely to have Externalizing Problems scores (OR = 4.6, 95% CI: 2.2-9.6) and three times more likely to have Total Problem scores (OR = 2.9, 95% CI: 1.4-6.1) in the clinical range on the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) when compared with children who did not receive a diagnosis of FASD (Stevens, Nash, Fantus, et al., 2013). With respect to psychiatric comorbidity, O’Connor and colleagues found that 87% of children exposed to alcohol prenatally met the criteria for a psychiatric disorder, with the majority exhibiting symptoms of mood disorder (61%) (O’Connor et al., 2002). Further, Burd and colleagues (Burd et al., 2003) found that 73% of
children with FASD had comorbid ADHD and 17.5% had comorbid ODD. These investigators also found that 25% of children with FASD had anger problems and 38.4% had poor social skills. When taken together, it is clear that prenatal alcohol exposure results in maladaptive behaviors and high rates of psychiatric disorders.

1.2.6 Existing neurodevelopmental profiles of FASD

In an effort to improve the screening for and diagnosis of FASD, the identification of a distinct neurodevelopmental profile of FASD has received some attention. The notion that a distinctive neurodevelopmental profile exists in individuals with FASD was first proposed in the late 1990s by Streissguth and colleagues (Streissguth, Bookstein, Barr, Press, & Sampson, 1998). Since this time, two approaches have been taken to determine the pathognomonic neurodevelopmental features of FASD, namely the utilization of i) behavioral observations/ratings by parents/caregivers and ii) subtest scores from standardized test batteries assessing a variety of neurodevelopmental domains.

1.2.6.1 Neurodevelopmental profiles of FASD based on behavioral observations/ratings by parents/caregivers

The CBCL and the BRIEF have been used to identify a neurodevelopmental profile characteristic of FASD.

1.2.6.1.1 Child Behavioral Checklist (CBCL)

Nash and colleagues (Nash et al., 2006) sought to determine if a behavioral profile distinguishes children with FASD (diagnosed according to the 2005 Canadian diagnostic
guidelines; Chudley et al., 2005) from typically developing children and children with ADHD. The CBCL is a well-established standardized parent/caregiver questionnaire utilized for evaluating social competencies and behavioral problems in children 6 to 18 years of age and is comprised of a series of open ended questions and a rating scale of 113 behavioral descriptors. The authors utilized discriminant function analysis and Receiver Operating Characteristics curve analyses to determine sensitivity and specificity of different item combinations. Findings revealed that ten specific behavioral characteristics captured by the CBCL (Table 2) had the potential to differentiate between children with FASD and children with ADHD and typically developing control children, all 6 to 16 years of age. Specific item combinations (Table 3) resulted in 86% sensitivity and 82% specificity when children with FAS where compared to typically developing control children, and 70% to 81% sensitivity and 72% to 80% specificity when children with FAS where compared to children with ADHD.

Nash et al. (Nash, Koren, & Rovet, 2011) replicated their earlier study (Nash et al., 2006) using a larger sample and comparing children with FASD (diagnosed using the 2005 Canadian guidelines; Chudley et al., 2005) to children with ODD/CD, as well as children with ADHD and typically developing control children in order to establish the specificity of the 10-item screening tool. All children ranged in age from 6 to 18 years of age. Findings revealed that the tool differentiated children with FASD from control children with 98% sensitivity and 42% specificity, and from children with ADHD with 89% sensitivity and 42% specificity. However, sensitivity and specificity could not be determined for discriminating children with FASD from children with ODD/CD since only one item (“acts young”) significantly differentiated these groups.

From their preliminary investigations showing that certain behaviors had the potential to identify children with a high likelihood of having FASD, Nash and colleagues (Nash et al.,
2011; Nash et al., 2006) proposed using this 10-item questionnaire as a screening tool and coined it the “Neurobehavioral Screening Tool (NST)”. Based on the two studies discussed above (Nash et al., 2011; Nash et al., 2006), it was concluded that the NST has the potential to delineate children with FASD from children with ADHD and normally developing children. However, these two studies were limited in that they retrospectively extracted items from the fully administered CBCL, and their samples consisted of children aged 6 to 18 only. The former limitation is noteworthy given that the CBCL is scored on a three-point scale (i.e., “not true”, “somewhat or sometimes true”, and “very true or often true”); the authors of the NST collapsed the responses “somewhat or sometimes true” and “very true or often true” and this can affect the classification accuracy. The latter limitation means that the behaviors noted in the NST cannot be assumed to be reflective of children with FASD outside this age range (i.e., less than 6 and over 18 years of age).

Accordingly, Breiner, Nulman, and Koren (Breiner, Nulman, & Koren, 2013) conducted a study in order to determine if the NST could be validated among a sample of children diagnosed with FASD (according to the 2005 Canadian Guidelines; Chudley et al., 2005), children with either a deferred diagnosis or for whom a diagnosis could not be confirmed, and normally developing control children, all 4 to 6 years of age. Three items (lie/cheat, steal at home, and steal outside the home) were excluded from the analysis due to the inability to verify these items in most young children. Using the seven remaining items, the authors found that the NST had 94% sensitivity and 96% specificity in identifying children with FASD (Table 3). However, it is unclear from which group children with FASD were discriminated (i.e., if the non-diagnosed group was combined with the control children), as the methods and results sections describing it are inadequate. Further, this study retrospectively extracted items from the CBCL in its entirety.
Table 2. Neurobehavioral Screening Tool (NST)

<table>
<thead>
<tr>
<th>Items</th>
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<tbody>
<tr>
<td>1. Has your child been seen or accused of or thought to have acted too young for his or her age?</td>
</tr>
<tr>
<td>2. Has your child been seen or accused of or is thought to be disobedient at home?</td>
</tr>
<tr>
<td>3. Has your child been seen or accused of or is thought to lie or cheat?</td>
</tr>
<tr>
<td>4. Has your child been seen or accused of or is thought to lack guilt after misbehaving?</td>
</tr>
<tr>
<td>5. Has your child been seen or accused of or is thought to have difficulty concentrating, and can’t pay attention for long?</td>
</tr>
<tr>
<td>6. Has your child been seen or accused of or is thought to act impulsively and without thinking?</td>
</tr>
<tr>
<td>7. Has your child been seen or accused of or is thought to have difficulty sitting still, is restless or hyperactive?</td>
</tr>
<tr>
<td>8. Has your child been seen or accused of or is thought to display acts of cruelty, bullying or meanness to others?</td>
</tr>
<tr>
<td>9. Has your child been seen or accused of or is thought to steal items from home?</td>
</tr>
<tr>
<td>10. Has your child been seen or accused of or is thought to steal items from outside of the home?</td>
</tr>
</tbody>
</table>

Source: (Nash et al., 2011; Nash et al., 2006)

*Note.* Each item has a response option of ‘Yes’ or ‘No’.
More recently, LaFrance et al. (LaFrance et al., 2014) administered the NST as a stand-alone instrument to parents/caregivers of children 6 to 17 years of age and thus, addressed the limitation of collapsing items originally scored on a three-point scale (Breiner et al., 2013; Nash et al., 2011; Nash et al., 2006). Using the scoring approach published by Nash and associates (Nash et al., 2006), compared with normally developing control children, the NST yielded 63% sensitivity and 100% specificity for children with FASD (diagnosed according to the 4-Digit Diagnostic Code; Astley, 2004) and 50% sensitivity and 100% specificity for children prenatally exposed to alcohol who did not meet the diagnostic threshold when assessed (Table 3). This study also assessed possible age- and sex-related differences on the NST, by comparing 6- to 11-year old children with 12- to 17-year old adolescents, and boys versus girls. For both the FASD group and the group of children prenatally exposed to alcohol who did not meet the diagnostic threshold, the NST showed higher sensitivity among adolescents (71% for both groups) than children (54% and 40%, respectively). For the FASD group only, the NST also had higher sensitivity among boys than girls (71% and 56%, respectively). Specificity was found not to differ with respect to age and sex, as it was 100% in all of the comparisons. Lastly, the authors explored an alternative cumulative scoring option, with the endorsement of at least four items resulting in 90% sensitivity and 91% specificity. This study is not only the first to administer the NST as a stand-alone instrument but is also the first to differentiate children prenatally exposed to alcohol who do not meet the criteria for an FASD diagnosis from typically developing control children. The discrimination of children prenatally exposed to alcohol who did not meet the criteria for an FASD diagnosis helps to further establish the specificity and discriminate validity of the NST. Nonetheless, it must be noted that this study involved the retrospective administration of the NST in a sample of children that had had already undergone a full diagnostic evaluation, thereby limiting the degree to which the results can be said to establish the validity of the NST as a “screening” tool per se.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age range</th>
<th>Comparison</th>
<th>Items endorsed</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Breiner et al., 2013)</td>
<td>4 to 6</td>
<td>FASD (n=17) vs. Deferred/Controls (n=43)</td>
<td>≥5 items (items 1, 2, 4-8; acts young, disobedient, lacks guilt, difficulty concentrating, impulsivity, hyperactive, cruelty)</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>(Haynes, Nulman, &amp; Koren, 2014)</td>
<td>6 to 12</td>
<td>Children born to and reared by mothers with depression (n=49) vs. Controls (n=22)</td>
<td>≥6 items (out of items 1-7; acts young, disobedient, lie/cheat, lacks guilt, difficulty concentrating, impulsivity, hyperactive) OR ≥3 items (out of items 1, 2, 3, and 4; acts young, disobedient, lie/cheat, lacks guilt)</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>(LaFrance et al., 2014)</td>
<td>6 to 17</td>
<td>FASD (n=48) vs. Controls (n=32)</td>
<td>≥6 items (out of items 1-7; acts young, disobedient, lie/cheat, lacks guilt, difficulty concentrating, impulsivity, hyperactive) OR ≥3 items (out of items 1, 2, 3, and 4; acts young, disobedient, lie/cheat, lacks guilt)</td>
<td>63%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children prenatally exposed to alcohol</td>
<td>≥6 items (out of items 1-7; acts young, disobedient, lie/cheat, lacks guilt, difficulty)</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Reference</td>
<td>Age range</td>
<td>Comparison</td>
<td>Items endorsed</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>-----------</td>
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<td>------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>(years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Nash et al., 2006)</td>
<td>6 to 18</td>
<td>FASD (n=30) vs. Controls (n=30)</td>
<td>≥6 items (out of items 1-7; acts young, disobedient, lie/cheat, lacks guilt, difficulty concentrating, impulsivity, hyperactive)</td>
<td>86%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FASD (n=30) vs. ADHD (n=30)</td>
<td>≥2 items (out of items 1, 4, and 8; acts young, lacks guilt, cruelty)</td>
<td>70%</td>
<td>80%</td>
</tr>
<tr>
<td>(Nash et al., 2011)</td>
<td>6 to 18</td>
<td>FASD (n=56) vs. Controls (n=53)</td>
<td>≥3 items (out of all 10 items; acts young, disobedient, lie/cheat, lacks guilt, difficulty concentrating, impulsivity, hyperactive, cruelty, steals from home, steals from outside home)</td>
<td>98%</td>
<td>42%</td>
</tr>
<tr>
<td>Reference</td>
<td>Age range (years)</td>
<td>Comparison</td>
<td>Items endorsed</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>-----------</td>
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<td>-------------</td>
</tr>
<tr>
<td>FASD (n=56) vs. ADHD (n=50)</td>
<td>≥2 items (out of items 1, 4, 8, 9, and 10; acts young, lacks guilt, cruelty, steals from home, steals from outside home)</td>
<td>89%</td>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FASD (n=56) vs. ODD/CD (n=61)</td>
<td>1 item (item 1; acts young)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; CI: Confidence Interval; FASD: Fetal Alcohol Spectrum Disorder; ODD: Oppositional Defiant Disorder

a It is assumed that children with FASD were compared to children for whom a diagnosis could not be confirmed or was deferred in combination with control children (methods and results sections were inadequate to determine if this assumption is correct)

b Items 3, 9, and 10 (lie/cheat, steal at home, and steal outside the home) were excluded from the analysis due to the inability to verify these items in most young children
In order to further establish the specificity of the NST, Haynes, Nulman, and Koren (Haynes et al., 2014) recently evaluated the influence of maternal depression – the most prevalent psychiatric morbidity among women with difficulties inhibiting their consumption of alcohol during pregnancy (Procopio et al., 2013) – on the previously identified behavioral presentation of children with FASD (LaFrance et al., 2014; Nash et al., 2011; Nash et al., 2006; diagnosed according to either the 2005 Canadian diagnostic guidelines [Chudley et al., 2005] or the 4-Digit Diagnostic Code [Astley, 2004]). Specifically, the investigators sought to determine if the NST resulted in any false positives among a sample of children born to and reared by mothers with clinical depression and typically developing control children. None of the children with mothers suffering from depression scored positive on the NST (100% specificity; Table 3). In fact, only one item (hyperactive) was found to be significantly higher in the group of children with mothers suffering from depression, compared with the control children.

In summary, the NST has demonstrated good sensitivity (63% to 98%), but varying specificity (42% to 100%, with some estimates being unfavorably low), and thus should still be considered in the validation stage. It is important to note that the NST is intended for screening purposes only (Nash et al., 2011; Nash et al., 2006), and given that it is limited to overt behaviors only, its ability as a diagnostic tool is questionable since it does not fully capture all neurodevelopmental impairments seen among individuals with FASD. Moreover, there are few limitations of the available studies on the NST that should be noted. First, all of the studies evaluating the psychometric utility of the NST are plagued by small or modest at best, clinically-referred Canadian samples, thus limiting generalizability of the above findings. Second, the NST has the inherent problem of providing the behavioral observations of parent or parent substitutes, who by definition are not masked to the child’s history and thus convey observations distorted by positive intent. Third, although a few of
the studies investigating the NST specified whether the participants that made up the comparison groups were screened for prenatal alcohol exposure, and subsequently excluded (Nash et al., 2011; Nash et al., 2006), others did not (Breiner et al., 2013; Haynes et al., 2014; LaFrance et al., 2014).

1.2.6.1.2 Behavior Rating Inventory of Executive Function (BRIEF)

Recently, Nguyen and colleagues (Nguyen et al., 2014) sought to determine whether the BRIEF (Gioia, Isquith, Guy, & Kenworthy, 2000) clinical scales, a parent/caregiver questionnaire that consists of 86-items and eight empirically derived clinical scales assessing executive function and self-regulation in children 5 to 18 years of age, can distinguish among the following four groups of children: 79 children prenatally alcohol-exposed with ADHD; 36 children prenatally alcohol-exposed without ADHD; 90 children with idiopathic ADHD (without prenatal alcohol exposure); and 168 typically developing control children. Prenatal alcohol exposure was defined as at least four drinks per occasion at least once per week or at least 14 drinks per week during pregnancy. A discriminant function analysis revealed that the following four clinical scales best distinguished the groups. i) Inhibit, which describes a child’s the ability to tune out irrelevant stimuli; ii) Emotional Control, which describes a child’s ability to modulate emotional responses; iii) Working Memory, which describes a child’s ability to hold information in mind for the purpose of completing a task; and iv) Organization of Materials, which describes a child’s orderliness of work, play, and storage spaces. Classification accuracy was 71% overall, with 67% of children prenatally alcohol-exposed with ADHD, 43% children prenatally alcohol-exposed without ADHD, 51% of children with idiopathic ADHD, and 92% of typically developing control children classified correctly.
Although its use as tool to discriminate individuals with FASD from other clinical populations is still in the exploratory stages, the BRIEF appears to distinguish alcohol-exposed children with ADHD from those with idiopathic ADHD, and thus may be useful as a screening tool. However, based on the results presented above, the ability of the BRIEF to identify children prenatally alcohol-exposed without ADHD is limited.

1.2.6.2 Neurodevelopmental profiles of FASD based on subtest scores from a battery of standardized tests

Mattson and colleagues (Mattson et al., 2010) sought to identify a neurodevelopmental profile of FASD using subtest scores from a battery of neurodevelopmental tests administered to individuals heavily exposed to alcohol prenatally, defined as four or more drinks per occasion at least once per week or 13 or more drinks per week, and individuals with no prenatal alcohol exposure or minimal exposure, defined as no more than one drink per week on average and a maximum of two drinks per occasion. All participants were between 7 and 21 years of age and subsequently categorized based only on physical features, regardless of their exposure status. Classifications included “FAS”, defined as the presence of at least two of the three key facial features (short palpebral fissures, smooth philtrum, and thin vermilion boarder) and either microcephaly (head circumference ≤10th percentile) or growth deficiency (weight and/or height ≤10th percentile) or both; “Not FAS”; or “Deferred”, defined as the presence of at least one key facial feature, or microcephaly and growth deficiency, or microcephaly or growth deficiency and at least one additional specified feature documented to be prevalent among those with FASD such as ptosis, and camptodactyly. Twenty-two variables, derived from the subtests of a battery of standardized tests, were selected based on their effect size in detecting the difference between exposed and unexposed individuals.
Two latent profile analyses were performed in order to derive a discriminative profile. In both analyses, a two-class solution fit better than a one-class solution – meaning that, based on the response means, it was more likely that there were two unobserved groups in the sample used in each analysis. In the first analysis, exposed individuals who met the study criteria for FAS (n=41) were compared with unexposed individuals categorized as Not FAS (n=46); the resulting profile had an overall classification accuracy of 92%, with 88% sensitivity and 96% specificity. In the second analysis, exposed individuals categorized as Not FAS or Deferred (n=38) were compared with unexposed individuals categorized as Not FAS or Deferred (n=60); the resulting profile had an overall classification accuracy of 85%, with 68% sensitivity and 95% specificity. The discriminative profile consisted of deficits in executive function, attention, spatial reasoning and memory, fine motor speed, and visual motor integration (Table 4). In both analyses, individuals categorized as belonging to “Group 1” performed more poorly than those belonging to “Group 2”, with significantly more alcohol-exposed individuals in “Group 1” and significantly more unexposed individuals in “Group 2”. See Table 4 for the measures included in the profile and neurodevelopmental domains assessed.

In a subsequent study, Mattson and colleagues (Mattson et al., 2013) attempted to further refine their initial neurodevelopmental profile (Mattson et al., 2010) by reducing the number of variables included, using a larger sample between 8 and 17 years of age, and including a clinical contrast group. The same definitions of “heavily exposed to alcohol prenatally” and “no prenatal alcohol exposure or minimal exposure” were used as before (Mattson et al., 2010). Based on clinical judgment and expertise, researchers selected 11 variables from the large test battery, four of which overlapped with those selected in the previous study (Mattson et al., 2010; overlapping measures are indicated with an asterisk in Table 5).
Table 4. Measures included in the profile and neurodevelopmental domains assessed by Mattson and colleagues (2010)

<table>
<thead>
<tr>
<th>Observed variable/measure</th>
<th>Neurodevelopmental domain(s) measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTAB Spatial Recognition Memory Percent Correct (z-score)</td>
<td>Visual memory, spatial reasoning</td>
</tr>
<tr>
<td>CANTAB Spatial Span Length (z-score)</td>
<td>Executive function, spatial reasoning, visual memory</td>
</tr>
<tr>
<td>CANTAB Spatial Working Memory Strategy (z-score)</td>
<td>Executive function, spatial working memory</td>
</tr>
<tr>
<td>CANTAB Spatial Working Memory Total Errors (z-score)</td>
<td>Executive function, spatial working memory</td>
</tr>
<tr>
<td>D-KEFS Trail Making Combined Number/Letter (scaled score)</td>
<td>Executive function, sequencing</td>
</tr>
<tr>
<td>D-KEFS Trail Making–Switch versus Number (scaled score)</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>D-KEFS Trail Making–Switch versus Visual (scaled score)</td>
<td>Executive function</td>
</tr>
<tr>
<td>D-KEFS Trail Making–Switch Errors (scaled score)</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Total Correct Letter (scaled score)</td>
<td>Executive function, fluency</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Total Correct Category (scaled score)</td>
<td>Executive function, fluency</td>
</tr>
<tr>
<td>Observed variable/measure</td>
<td>Neurodevelopmental domain(s) measured</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Total Correct Switch (scaled score)</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Second Interval Correct (scaled score)</td>
<td>Executive function, fluency</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Set Loss Errors (scaled score)</td>
<td>Executive function, set maintenance</td>
</tr>
<tr>
<td>MVWM Time in Target Quadrant on Probe Trail (raw score)</td>
<td>Spatial learning</td>
</tr>
<tr>
<td>NES3 Animals Following subtest, Number Correct (raw score)</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>NES3 Animals Repeating subtest, Number Correct (raw score)</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>NES3 Animals Single subtest, Number Correct (raw score)</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>Grooved Pegboard Test Dominant Hand Completion Time (z-score)</td>
<td>Fine motor</td>
</tr>
<tr>
<td>Grooved Pegboard Test Non-Dominant Hand Completion Time (z-score)</td>
<td>Fine motor</td>
</tr>
<tr>
<td>Progressive Planning Test Maximally Constrained Total Score (raw score)</td>
<td>Executive function, planning</td>
</tr>
<tr>
<td>Visual Discrimination Reversal Learning Test Number of Reversals (raw score)</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>Visual Motor Integration Test Total (standard score)</td>
<td>Visual-motor</td>
</tr>
</tbody>
</table>

CANTAB: Cambridge Neuropsychological Test Automated Battery; D-KEFS: Delis-Kaplan
Three latent profile analyses were conducted. In all three analyses, a two-class solution fit better than a one-class solution. In the first analysis, exposed individuals who met the study criteria for FAS (same criteria as the authors previous study (Mattson et al., 2010); n=79) were compared with unexposed individuals (n=185) and the resulting profile yielded an overall classification accuracy of 76%, with 77% sensitivity and 76% specificity. In the second analysis, exposed individuals who did not meet the criteria for FAS (n=117) were compared with unexposed individuals (n=185); the resulting profile had an overall classification accuracy of 72%, with 70% sensitivity and 72% specificity. The third analysis comparing exposed individuals with and without FAS (n=209) and individuals with ADHD who were not exposed to alcohol prenatally (as per the definition of prenatal alcohol exposure used by the authors; n=74) led to a profile with an overall classification accuracy of 74%, with 60% sensitivity and 76% specificity. The discriminative profile consisted of deficits in executive function, attention, and visual and spatial memory, with measures of executive function most effectively distinguishing individuals prenatally alcohol-exposed from those not exposed (Table 5). In all three analyses, significantly more alcohol-exposed individuals belonged to “Group 1” and significantly more unexposed individuals to “Group 2” (see Table 5 for the measures included in the profile and neurodevelopmental domains assessed).

From a clinical perspective, the psychometric utility of the profile of Mattson and colleagues (Mattson et al., 2013) was not optimal in discriminating those with FASD from those with ADHD – it was more accurate at identifying individuals with ADHD than individuals with
FASD. Further, it appears that a more limited test battery is not equally as useful at distinguishing between individuals with FASD and unexposed individuals as a larger test battery, as the sensitivity was reduced from 88% in the first study (Mattson et al., 2010) to 77% in the second study (Mattson et al., 2013). Lastly, although the classification rates were significant, a number of subjects were misclassified. Further, the two studies by Mattson et al. (Mattson et al., 2010; Mattson et al., 2013) have a few limitations to note. First, coupled with the fact that the authors utilized test batteries that accommodated the large age range and language variations of their samples, the batteries used do not constitute a full clinical assessment battery typically used in an FASD diagnostic clinics. As such, the test batteries lacked clinical sensitivity and likely excluded other measures that may have been useful in distinguishing individuals with FASD from unexposed controls and other clinical populations. Second, the samples were made up of participants clinically referred for suspected problems or exposures and thus prone to sampling bias, undermining the external validity of the findings. Third, the investigators only included weaknesses in their neurodevelopmental profile and did not include relative strengths. Fourth, the classification of individuals as having FAS was based on physical traits only and is not reflective of how FAS is classified elsewhere (see for example, the criteria of the Canadian guidelines for diagnosis; Table 1).

Recently, Enns and Taylor (Enns & Taylor, 2018) used logistic regression to determine which neurodevelopmental variables are most predictive of an FASD diagnosis. Studied were 180 children and adolescents (5.8 to 17.8 years of age) prenatally exposed to alcohol, 107 of whom received a diagnosis of FASD according to the 2005 Canadian diagnostic guidelines (Chudley et al., 2005) and 73 who did not. The authors identified a model that incorporated specific intelligence indices (verbal intelligence and working memory), academic achievement (spelling and math calculations), auditory working memory, and spatial planning that correctly classified 75% of cases (sensitivity and specificity were not
reported). However, it was not clear if scaled scores were used in the model, and the most obvious limitation of the study is that data were retrospectively collected via a chart review of a clinically referred sample. Further, given the retrospective nature of the study, the number of children and adolescents assessed using each measure varied – however, the sample size was not specified for the final profile. Although the identified profile was able to differentiate individuals diagnosed with FASD from those who were prenatally exposed to alcohol but whom did not receive a diagnosis of FASD, the ability to differentiate individuals with FASD from unexposed individuals and individuals with other clinical populations remains unclear. See Table 6 for the measures included in the profile and neurodevelopmental domains assessed by Enns and Taylor (Enns & Taylor, 2018).

1.2.6.3 Summary

Based on the studies reviewed above, it is clear that a definitive neurodevelopmental profile of FASD has yet to be identified. However, the current literature has notable clinical implications. First, behavioral ratings by primary caregivers have the potential to be used in the development of a screening tool, which can be used to identify those children most in need of a full multi-disciplinary diagnostic assessment. Second, a battery of neurodevelopmental tests can be used to distinguish between children with FASD and typically developing children, children prenatally exposed to alcohol but who do not meet the criteria for a diagnosis of FASD, as well as children with ADHD. Overall, the results of the current literature support a stepwise approach the diagnosing of FASD – i.e., screening, followed by a full diagnostic assessment for those screened positive. As discussed above, a diagnosis of FASD has a number of important benefits namely, participation in developmental interventions, improved quality of life and a more prosperous developmental trajectory in terms of social functioning. Although a biomarker would be the most ideal
method for diagnosing cases of FASD, at this time observational data and
neurodevelopmental testing are the most appropriate tools. Thus, the identification of a
distinct neurodevelopmental profile that is pathognomonic of FASD will assist in the: i) accurate identification of individuals with FASD, by adding to the resources available to clinicians; ii) discrimination of FASD from other clinical populations (i.e., differential diagnosis); iii) ascertaining accurate prevalence estimates; iv) planning/development of appropriate targeted interventions for individuals with FASD; and v) enhancement of clinical services to this population. Coupled with the fact that the neurodevelopmental assessment is both time consuming and costly (Popova et al., 2013), the current capacity of diagnostic services is also limited (Clarren, Lutke, & Sherbuck, 2011). Thus, delineating the specific neurodevelopmental profile of FASD will not only reduce the time it takes to fully assess an individual, but it will also assist in triaging children most in need of a full clinical assessment (Nash et al., 2011; Nash et al., 2006).

Nevertheless, studies utilizing observational and/or neurodevelopmental data to identify the presence of a unique neurodevelopmental profile of FASD are not without their limitations (e.g., confounding, and a lack of normative data with respect to FASD and mixed racial groups). In addition to the inherent data limitations, the two approaches currently used in determining the neurodevelopmental profile of FASD are both limited in scope. For instance, the approach involving observations/ratings of parents/caregivers is solely based on problem behaviors. However, individuals with FASD have a number of other developmental impairments and behavioral manifestations that could be useful when delineating FASD from other clinical populations. Further, the neurodevelopmental profiles based on the subtest scores from a battery of standardized tests do not consider the relative strengths of individuals with FASD (Greenbaum, Nulman, Rovet, & Koren, 2002; Mattson et al., 2011).
Table 5. Measures included in the profile and neurodevelopmental domains assessed by Mattson and colleagues (2013)

<table>
<thead>
<tr>
<th>Observed variable/measure</th>
<th>Neurodevelopmental domain(s) measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTAB Delayed Matching to Sample Percent Correct (z-score)</td>
<td>Short-term and long-term visual and spatial memory</td>
</tr>
<tr>
<td>CANTAB Intra-Extra Dimensional Shift Stages Completed (z-score)</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>CANTAB Intra-Extra Dimensional Shift Total Errors (z-score)</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>CANTAB Simple Reaction Time Percent Correct Trials (raw score)</td>
<td>Attention, reaction time</td>
</tr>
<tr>
<td>CANTAB Spatial Working Memory Total Errors (z-score)*</td>
<td>Executive function, spatial working memory</td>
</tr>
<tr>
<td>D-KEFS Color-Word Interference Inhibition/Switching (scaled score)</td>
<td>Executive function, inhibitory control, cognitive flexibility</td>
</tr>
<tr>
<td>D-KEFS Trail Making–Switch versus Number (scaled score)*</td>
<td>Executive function, cognitive flexibility</td>
</tr>
<tr>
<td>D-KEFS 20 Questions Total Initial Abstraction (scaled score)</td>
<td>Executive function, planning, deduction</td>
</tr>
<tr>
<td>D-KEFS Tower Test Rule Violations Per Item Ratio (scaled score)</td>
<td>Executive function, planning</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Total Correct Letter (scaled score)*</td>
<td>Executive function, fluency</td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Total Correct Switch (scaled score)*</td>
<td>Executive function, cognitive</td>
</tr>
<tr>
<td>Observed variable/measure</td>
<td>Neurodevelopmental domain(s) measured</td>
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<td>---------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>score)*</td>
<td>flexibility</td>
</tr>
</tbody>
</table>

*Indicates the measures that overlap with those selected in (Mattson et al., 2010)

CANTAB: Cambridge Neuropsychological Test Automated Battery; D-KEFS: Delis-Kaplan Executive Function System.

Table 6. Measures included in the profile and neurodevelopmental domains assessed by Enns and Taylor (2018)

<table>
<thead>
<tr>
<th>Observed variable/measure</th>
<th>Neurodevelopmental domain(s) measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS Stories: Delayed/WMS-IV Logical Memory II</td>
<td>Auditory working memory</td>
</tr>
<tr>
<td>D-KEFS Tower: Total Achievement</td>
<td>Executive function, spatial planning</td>
</tr>
<tr>
<td>WISC-IV Working Memory Index</td>
<td>Working memory</td>
</tr>
<tr>
<td>WISC-IV Verbal Comprehension Index</td>
<td>Verbal intelligence</td>
</tr>
<tr>
<td>WRAT4 Math Calculations</td>
<td>Academic achievement, mathematical ability</td>
</tr>
<tr>
<td>WRAT4 Spelling</td>
<td>Academic achievement, basic reading and spelling ability</td>
</tr>
</tbody>
</table>

It should also be recognized that the studies reviewed used different diagnostic guidelines for ascertaining cases of FASD. Given that it was recently reported that existing FASD diagnostic guidelines lack convergent validity and are limited in their concordance with respect to the specific diagnostic entities (Coles et al., 2016), the consequence of this variation is that the profiles are essentially classifying different groups of affected individuals. Thus, the only conceivable way to resolve this issue is for a standardized common diagnostic approach to be developed and widely accepted. Only then will we be able to identify whether a neurodevelopmental profile of FASD exists, and truly assess its classification function.

Further, given the stigmatization associated with alcohol use during pregnancy and the increased likelihood of underreporting (Lange, Shield, Koren, Rehm, & Popova, 2014), it is possible that the comparison groups of typically developing control children used in the studies reviewed may contain some children prenatally exposed to alcohol, which is possible for example in studies of Mattson and colleagues (Mattson et al., 2010; Mattson et al., 2013) given their definition of prenatal alcohol exposure. Consequently, the classification function of a particular profile could in fact be more robust than observed.

Although it is clear that the identification of a neurodevelopmental profile of FASD has a number of notable benefits, at least eight areas of future research need to be addressed before a neurodevelopmental profile is defined and put into practice. The first concerns testing the profile on larger, more diverse samples, as well as in general population screening settings (i.e., among population-based samples). Second, the profile’s ability to differentiate children with FASD from other clinical populations (for example, other than idiopathic ADHD, without prenatal alcohol exposure) needs to be determined. Third, potential gender and age differences need to be explored, and the cross-cultural utility of the
One of the major challenges in the study of FASD is to establish a comprehensive profile of neurodevelopmental domains affected by prenatal alcohol exposure. Fourth, a broader, more comprehensive array of neurodevelopmental domains needs to be evaluated. Fifth is the possibility that individuals with FASD exhibit more than one neurodevelopmental profile should be explored. For example, a distinct profile could exist for each diagnostic category. Sixth, future studies need to control for adverse prenatal exposures such as maternal smoking and drug use during pregnancy, maternal and paternal psychopathologies, and postnatal experiences including abuse and neglect. Seventh is the possibility that some of the associated neurodevelopmental symptoms were inherited from parents (for example, a math disability) and not strictly attributable to the prenatal alcohol exposure. Eighth, it is possible that individual differences in factors that influence the consequences of prenatal alcohol exposure may interfere with the identification of a unique neurodevelopmental profile of FASD given that susceptibility to prenatal alcohol exposure depends on the genotype of the fetus (Eberhart & Parnell, 2016) and the developmental stage at the time of exposure, and that the manifestations of abnormal development increase in frequency and degree as dosage increases (as per the principles of teratogenesis) (O’Leary-Moore, Parnell, Lipinski, & Sulik, 2011; Sulik, 2014). Accordingly, genetic factors/differences in fetal susceptibility to alcohol and information on dosage and timing of exposure should also be taken into consideration when identifying and validating a neurodevelopmental profile of FASD. It is likely that many of these areas of future research will only be achievable if and when large detailed datasets are developed containing data on individuals with FASD diagnosed using a common diagnostic guideline, which will allow for certain variables (for example, experience of postnatal adversities) to be controlled for.

However, given that the outcomes of prenatal alcohol exposure depend on a number of factors (for example, genetics, health, alcohol metabolism, polysubstance exposure, timing of exposure) (Day, Savani, Krempley, Nguyen, & Kitlinska, 2016; Eberhart & Parnell, 2016;...
May & Gossage, 2011), as well as the fact that FASD is associated with multiple comorbid mental disorders (Burd et al., 2003; Popova et al., 2016), it should be acknowledged that FASD may in fact have a complex phenotype and a pathognomonic neurodevelopmental profile of FASD may not exist. It is possible that FASD has a pleiotropic phenotype (i.e., one cause – prenatal alcohol exposure – results in many outcomes); if this is the case it will challenge the existence of a neurodevelopmental profile unique to those with FASD.

In conclusion, although research in this area is limited and a definitive neurodevelopmental profile of FASD remains to be established, the benefits of identifying a pathognomonic neurodevelopmental profile are noteworthy. It is likely that a neurodevelopmental profile of FASD that includes both behavioral observations/ratings and performance-based measures of neurodevelopment will be the most comprehensive and as such, future studies should include measures covering a broad array of neurodevelopmental and behavioral domains.
Chapter 2 Aims and Hypotheses
2.1 Objective

The overall objective of the current thesis project was two-fold, to i) determine to what extent neurodevelopmental disorders, namely externalizing disorders, co-occur among individuals with FASD; and ii) determine if children with FASD exhibit a unique and discernible neurodevelopmental profile, compared to a) typically developing control children and b) children with other neurodevelopmental disorders.

For the purposes of the current thesis project, a neurodevelopmental profile of FASD was defined as the outward expression (behavioral and developmental) of the central nervous system damage caused by prenatal alcohol exposure.

2.2 Specific Aims and Hypotheses

2.2.1 Specific Aim I

To estimate the prevalence of neurodevelopmental disorders with prominent externalizing behaviors, namely ADHD, CD, ODD, as well as Autism Spectrum Disorder (ASD) 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).

Hypothesis 1

Neurodevelopmental disorders with prominent externalizing behaviors occur at a higher rate among children with FASD, when compared with the general population.
2.2.2 Specific Aim II

To determine if a neurodevelopmental profile of FASD exists that can differentiate children with FASD from typically developing control children.

Hypothesis 2a
Children with FASD will exhibit a neurodevelopmental profile that will differentiate them from typically developing control children with a high degree of accuracy.

Hypothesis 2b
Children with FASD will perform at a lower level across all subtests included in the neurodevelopmental profile (reflective of a generalized cognitive deficit), compared to typically developing control children.

Hypothesis 2c
Children with FASD will receive a higher score on the behavioral measures included in the neurodevelopmental profile, compared to typically developing control children.

2.2.3 Specific Aim III

To test whether the identified neurodevelopmental profile is unique to children with FASD and able to differentiate children with FASD from children with other neurodevelopmental disorders.
Hypothesis 3

Children with FASD will exhibit a distinct neurodevelopmental profile that allows for them to be clearly differentiated from children with other neurodevelopmental disorders.
Chapter 3 Prevalence of Externalizing Disorders and ASD Among Children with FASD

This chapter was modified from the following:
3.1 Background

The unifying outcome for FASD is congenital damage to the central nervous system, which is variably associated with a wide range of mental and behavioral disorders (Burd et al., 2003; Fryer et al., 2007; O'Connor et al., 2002; Popova et al., 2016). The mental and behavioral 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 behaviors that are directed toward the external environment and include aggression, anger, defiance, destruction of property, hostility, noncompliance and violations of social rules. These problematic behaviors are the core of a group of neurodevelopmental disorders known as externalizing disorders. Externalizing disorders consist of ADHD (DSM-5 code: 314.0X; ICD-10 code: F90.X), CD (DSM-5 code: 312.8X; ICD-10 code: F91.X) and ODD (DSM-5 code: 313.81; ICD-10 code: F91.3). The latter two consist of a persistent pattern of behavior that include: angry and irritable mood, argumentative and defiant behavior 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 behaviors are elevated in children with FASD (Mattson & Riley, 2000), who are often described as hyperactive, impulsive, disruptive and/or delinquent (Nash et al., 2006). Franklin and colleagues (Franklin, Deitz, Jirikowic, & Astley, 2008) found that among their sample of children with FASD, 75% scored in the “clinical” range on the externalizing problems scale of the CBCL. However, the presence of externalizing behaviors, 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 behavior 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 behaviors.

In addition to their behavioral impairments, children with externalizing disorders often have problems with their social and academic functioning. Although not an explicit externalizing disorder, ASD (DSM-5 code: 299.00; ICD-10 code: F84.0) is associated with high rates of externalizing behaviors (Mahan & Matson, 2011; Totsika, Hastings, Emerson, Lancaster, & Berridge, 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 (Bauminger, Solomon, & Rogers, 2010; Brereton, Tonge, & Einfeld, 2006; Matson, Wilkins, & Macken, 2008).

Given that externalizing behaviors are elevated in children with FASD, it is likely that rates of disorders with prominent externalizing behaviors 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).
3.2 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.

3.2.1 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, armd, 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*, occurrence*, 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 & 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/behavioral 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.

3.2.1.1 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 (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.

3.2.1.2 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.

3.2.1.3 Critical appraisal of existing studies

Each study was critically appraised using a tool specifically for use in systematic reviews addressing questions of prevalence (Munn, Moola, Riitano, & Lisy, 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.

3.2.2 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 & 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, Doi, Lee, Norman, & Vos, 2013; Rucker, Schwarzer, Carpenter, & Olkin, 2009), the data were transformed using the Freeman-Tukey double arcsine transformation (Freeman & Tukey, 1950). Score test-based 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 & 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, Davey Smith, Schneider, & Minder, 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.
3.2.3 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.

3.3 Results

3.3.1 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, Layton, Yacoub, & Turk, 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 employed is depicted in Figure 5.

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 7 for the study characteristics and the prevalence of ADHD, ASD, CD, and ODD among individuals with FASD reported in the individual studies.

3.3.1.1 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.
Figure 5. Schematic diagram depicting the search strategy employed.
3.3.2 Meta-analysis

3.3.2.1 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 8). For the forest plots of the prevalence of ADHD, ASD, CD, and ODD among children with FASD see Figure 6.

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 8). 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 8). See Figure 7 for the funnel plots of the prevalence of ADHD, ASD, CD, and ODD among children with FASD.

3.3.2.1.1 Sub-analyses

Neither population nor method of ascertainment were determined to be sources of heterogeneity in the disorder-specific estimates where heterogeneity was present (i.e., ADHD, CD, and ODD). See Table 9 for the results of the disorder-specific meta-analyses by population and by method of case ascertainment.
### Table 7. Study characteristics and prevalence of ADHD, ASD, CD, and ODD among children with FASD reported in the identified studies

<table>
<thead>
<tr>
<th>Reference; Country Year(s)</th>
<th>Study Population</th>
<th>Sample size; Diagnostic breakdown</th>
<th>Prevalence</th>
<th>FASD</th>
<th>Method of ascertain-ment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Astley, 2010); USA 1993-2005</td>
<td>General population</td>
<td>1270*; FASD = 59 FAS + 95 pFAS 394 SE/AE + 722 ND/AE</td>
<td>ADHD n (%) = 447 (57.3%) ASD n (%) = 42 (3.3%) CD n (%) = 119 (9.4%) ODD n (%) = -</td>
<td>FASD 4-digit</td>
<td>Passive: medical code (Astley &amp; Clarren, 1999)</td>
</tr>
<tr>
<td>(Bell et al., 2010); Canada n/a</td>
<td>General population</td>
<td>425; FASD = 86 FAS/pFAS + 339 ARND</td>
<td>ADHD n (%) = 200 (47.1%) ASD n (%) = 8 (1.9%) CD n (%) = -</td>
<td>FASD 4-digit</td>
<td>Passive: medical code (Chudley et al., 2005)</td>
</tr>
</tbody>
</table>
| (Burd et al., 2003); USA n/a | General population | 303; FASD = 152 FAS + 151 pFAS | ADHD n (%) = 219 (72.3%) ASD n (%) = - | FASD 4-digit | Passive: medical code (Burd &
<table>
<thead>
<tr>
<th>Reference; Country</th>
<th>Study Year(s)</th>
<th>Population</th>
<th>Sample size; Diagnostic breakdown</th>
<th>Prevalence</th>
<th>FASD</th>
<th>Method of ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CDC), USA 1981-1995</td>
<td>92</td>
<td>Aboriginal population</td>
<td>60; 60 FAS</td>
<td>12 (20.0%)</td>
<td>(Sokol &amp; Clarren, 1989)</td>
<td>Passive: medical records</td>
</tr>
<tr>
<td>(Chasnoff et al., 2015); USA</td>
<td>n/a</td>
<td>Foster and adopted children/youth</td>
<td>156; FASD = 93 FAS + 1 pFAS + 61 ARND + 1 ARBD</td>
<td>88 (56.4%) 8 (5.1%) 4 (2.6%)</td>
<td>(Astley &amp; Clarren, 1999)</td>
<td>Active: diagnostic code psychological assessment</td>
</tr>
<tr>
<td>(Chen, Olson, Picciano, Starr, &amp;</td>
<td>2007</td>
<td>General population</td>
<td>33; FASD = 5 FAS/pFAS + 21 ND/AE + 7 SE/AE</td>
<td>25 (75.8%)</td>
<td>(Astley &amp; Clarren, 1999)</td>
<td>Passive: diagnostic code parental reports</td>
</tr>
<tr>
<td>Reference; Country Year(s)</td>
<td>Study Population</td>
<td>Sample size; Diagnostic breakdown</td>
<td>Prevalence</td>
<td>FASD</td>
<td>Method of ascertain-ment</td>
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<tr>
<td>Owens, 2012; USA</td>
<td>(Clark, Lutke, Minnes, &amp; Ouellette-Kuntz, 2004); Canada</td>
<td>General population</td>
<td>FASD = 62; FAS = 34 FAS/probable FAS + 28</td>
<td>40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1999-2004; Norway</td>
<td>General population</td>
<td>FAS + 28</td>
<td>FAE/</td>
<td>probable</td>
<td>FAE</td>
</tr>
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<td></td>
<td>Elgen, Bruaroy, &amp; Laegreid, 2007; Norway</td>
<td>General population</td>
<td>FAS = 25 FAS + 22</td>
<td>(93.3%)</td>
<td>b</td>
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b: Excludes probable FAS/other-FASD.
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<tr>
<th>Reference; Country</th>
<th>Study Year(s)</th>
<th>Population</th>
<th>Sample size; Diagnostic breakdown</th>
<th>Prevalence</th>
<th>FASD</th>
<th>Method of ascertainment</th>
</tr>
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<tr>
<td>(Elliott et al., 2008); Australia 2001-04</td>
<td>General population</td>
<td>92; FASD = 25 FAS + 65 pFAS + 2 suspected FAS</td>
<td>11 (12.0%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Fryer et al., 2007); USA</td>
<td>n/a General population</td>
<td>39; n/a</td>
<td>37 (94.9%)</td>
<td>-</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>(Green et al., 2009); Canada</td>
<td>n/a General population</td>
<td>89; n/a</td>
<td>53 (59.6%)</td>
<td>2 (2.2%)</td>
<td>3 (3.4%)</td>
<td>19 (21.3%)</td>
</tr>
<tr>
<td>(Habbick, Nanson, Snyder, 1992-94) General population</td>
<td>207; n/a</td>
<td>68 (32.9%)</td>
<td>7 (3.4%)</td>
<td>-</td>
<td>10 (4.8%)</td>
<td>Guidelines by the Fetal Alcohol psychological assessment Active: psychological assessment</td>
</tr>
<tr>
<td>Reference; Country</td>
<td>Study Year(s)</td>
<td>Population</td>
<td>Sample size;</td>
<td>Prevalence</td>
<td>FASD Diagnostic breakdown</td>
<td>FASD Diagnostic criteria used</td>
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<tr>
<td>Casey, &amp; Schulman, 1996; Canada</td>
<td>(including Aboriginals)</td>
<td>1981-93 Aboriginal population</td>
<td>78; FASD = 43 FAS + 35 “incomplete” FAS</td>
<td>ADHD: 20 (25.6%)</td>
<td>ASD: 10 (12.8%)</td>
<td>n/a</td>
</tr>
<tr>
<td>(Kvine et al., 2004); USA</td>
<td>93</td>
<td>USA</td>
<td>43 FAS + 35</td>
<td>FASD = 78;</td>
<td>ADHD: 20</td>
<td>ASD: 10</td>
</tr>
</tbody>
</table>

*ADHD, ASD, CD, ODD, FASD:* ADHD, Autism Spectrum Disorder, Conduct Disorder, Oppositional Defiant Disorder, Fetal Alcohol Spectrum Disorder.
<table>
<thead>
<tr>
<th>Reference; Country</th>
<th>Study Year(s)</th>
<th>Population</th>
<th>Sample size; Diagnostic breakdown</th>
<th>Prevalence n (%)</th>
<th>FASD</th>
<th>Method of ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Landgren et al., 2010); Sweden</td>
<td>1998-2002</td>
<td>Adopted children (from Eastern Europe)</td>
<td>37; FASD = 21 FAS + 10 pFAS + 6 ARND</td>
<td>ADHD n (%) 21 (56.8%), ASD n (%) 2 (5.4%), CD n (%) 2 (5.4%), ODD n (%) 15 (40.5%)</td>
<td>Revised IOM criteria</td>
<td>Active: psychological assessment (Hoyme et al., 2005)</td>
</tr>
<tr>
<td>(Lewis et al., 2016); South Africa</td>
<td>n/a</td>
<td>General population</td>
<td>29; 29 FAS/pFAS</td>
<td>ADHD n (%) 9 (31.0%)</td>
<td>Revised IOM criteria</td>
<td>Active: psychological assessment (Hoyme et al., 2005)</td>
</tr>
<tr>
<td>(O'Connor et al., 2002); USA</td>
<td>n/a</td>
<td>General population</td>
<td>23; FASD = 2 FAS + 4 pFAS + 17 ARND</td>
<td>ADHD n (%) 3 (13.0%), ASD n (%) 1 (4.3%)</td>
<td>4-digit diagnostic code (Astley &amp; Clarren, 1999)</td>
<td>Active: psychological assessment</td>
</tr>
<tr>
<td>Reference; Country</td>
<td>Study Year(s)</td>
<td>Population</td>
<td>Sample size; Diagnostic breakdown</td>
<td>Prevalence</td>
<td>FASD</td>
<td>Method of ascertain- ment</td>
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<tr>
<td>(Rasmussen et al., 2010); Canada</td>
<td>2005-08</td>
<td>General population</td>
<td>52; FASD = 1</td>
<td>33 - - -</td>
<td>4-digit</td>
<td>Active: diagnostic code (Astley &amp; Clarren, 1999)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>FAS + 6</td>
<td>(63.5%)</td>
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<td></td>
<td></td>
<td>pFAS + 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ND/AE + 32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SE/AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Stevens, Nash, Koren, &amp; Rovet, 2013); Canada</td>
<td>n/a</td>
<td>General population</td>
<td>25; FASD = 5</td>
<td>16 - - 5</td>
<td>Canadian</td>
<td>Passive: medical records (Chudley et al., 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pFAS + 20</td>
<td>(64.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Stromland et al., 2015); Brazil</td>
<td>n/a</td>
<td>Children residing in orphanage</td>
<td>16; FASD = 3</td>
<td>6 - - 1</td>
<td>Revised IOM</td>
<td>Active: psychological assessment (Hoyme et al., 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FAS + 6</td>
<td>(37.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pFAS + 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference; Country</td>
<td>Study Year(s)</td>
<td>Population</td>
<td>Sample size;</td>
<td>Prevalence Diagnostic breakdown</td>
<td>FASD Diagnostic criteria used</td>
<td>Method of ascertainment</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>------------</td>
<td>--------------</td>
<td>---------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>(Williams et al., 2014); Canada</td>
<td>n/a</td>
<td>General population</td>
<td>31; n/a</td>
<td>22 n (%) (71.0%)</td>
<td>-</td>
<td>Canadian guidelines medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Chudley et al., 2005)</td>
</tr>
</tbody>
</table>

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; USA: United States of America

*The sample size for Astley (Astley, 2010) was 780 for ADHD, 1271 for CD, and 1268 for ODD*
Table 8. Pooled prevalence (results from meta-analysis) of ADHD, ASD, CD and ODD among children with FASD and results of the tests of heterogeneity and publication bias

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of included studies</th>
<th>Number of subjects</th>
<th>Pooled prevalence estimate</th>
<th>95% CI</th>
<th>I² (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>20</td>
<td>2,582</td>
<td>52.9%</td>
<td>43.7%</td>
<td>62.0%</td>
<td>94.6</td>
</tr>
<tr>
<td>ASD</td>
<td>6</td>
<td>1,029</td>
<td>2.6%</td>
<td>1.4%</td>
<td>4.1%</td>
<td>15.1</td>
</tr>
<tr>
<td>CD</td>
<td>5</td>
<td>1,514</td>
<td>7.0%</td>
<td>2.5%</td>
<td>13.2%</td>
<td>80.8</td>
</tr>
<tr>
<td>ODD</td>
<td>11</td>
<td>2,719</td>
<td>12.9%</td>
<td>8.4%</td>
<td>18.2%</td>
<td>89.0</td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

*Regression test

3.3.3 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, Chiu, Demler, Merikangas, & Walters, 2005), 1.5% for ASD (versus 2.6%) (Christensen et al., 2016), 2.7% for CD (versus 7.0%) (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), and 2.7% for ODD (versus 12.9%) (Costello et al., 2003). See Figure 8 for the prevalence of ADHD, ASD, CD, and ODD among children with FASD and without FASD (i.e., the general population).
Figure 6. Forest plot of the prevalence of ADHD (A), ASD (B), CD (C) and ODD (D) among children with FASD reported in the studies included in meta-analysis.

CI: confidence interval.

Note. The size of the box around the point estimate is representative of the weight of the estimate used in calculating the pooled point estimate.
3.4 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 (Lange, Probst, Gmel, 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, Lange, Burd, & Rehm, 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 (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...
Figure 7. Funnel plot of the prevalence of ADHD (A), ASD (B), CD (C) and ODD (D) among children with FASD reported in the studies included in meta-analysis.
Table 9. Sub-analyses of the pooled prevalence (results from meta-analysis) of ADHD, CD and ODD among children with FASD by population and method of ascertainment and results of the tests of heterogeneity and publication bias

<table>
<thead>
<tr>
<th>Diagnosis; Population; Method of ascertainment</th>
<th>Number of included studies</th>
<th>Number of subjects</th>
<th>Pooled prevalence estimate</th>
<th>95% CI</th>
<th>I²</th>
<th>P-value (regression test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>15</td>
<td>2,235</td>
<td>57.5%</td>
<td>46.8%</td>
<td>67.8%</td>
<td>95.2%</td>
</tr>
<tr>
<td>Aboriginal population</td>
<td>2</td>
<td>138</td>
<td>23.1%</td>
<td>16.4%</td>
<td>30.6%</td>
<td>-</td>
</tr>
<tr>
<td>Children in care</td>
<td>3</td>
<td>209</td>
<td>55.1%</td>
<td>47.9%</td>
<td>62.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td><strong>Method of ascertainment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>7</td>
<td>520</td>
<td>42.1%</td>
<td>29.4%</td>
<td>55.4%</td>
<td>86.2%</td>
</tr>
<tr>
<td>Passive</td>
<td>13</td>
<td>2,062</td>
<td>58.5%</td>
<td>46.7%</td>
<td>69.8%</td>
<td>95.8%</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>3</td>
<td>1,399</td>
<td>5.8%</td>
<td>1.2%</td>
<td>13.1%</td>
<td>81.3%</td>
</tr>
<tr>
<td><strong>Method of ascertainment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive</td>
<td>4</td>
<td>1,477</td>
<td>7.5%</td>
<td>2.3%</td>
<td>15.0%</td>
<td>85.3%</td>
</tr>
<tr>
<td>Diagnosis; Population; Method of ascertainment</td>
<td>Number of included studies</td>
<td>Number of subjects</td>
<td>Pooled prevalence estimate</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
<td>I²</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------</td>
<td>-------------------</td>
<td>----------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>----</td>
</tr>
<tr>
<td>ODD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>8</td>
<td>2,418</td>
<td>13.0%</td>
<td>8.6%</td>
<td>18.1%</td>
<td>87.2%</td>
</tr>
<tr>
<td>Children in care</td>
<td>3</td>
<td>209</td>
<td>13.0%</td>
<td>0.0%</td>
<td>45.2%</td>
<td>94.0%</td>
</tr>
<tr>
<td>Method of ascertainment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>4</td>
<td>416</td>
<td>10.0%</td>
<td>1.2%</td>
<td>24.4%</td>
<td>91.2%</td>
</tr>
<tr>
<td>Passive</td>
<td>7</td>
<td>2,211</td>
<td>14.7%</td>
<td>9.8%</td>
<td>20.4%</td>
<td>86.5%</td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

*Regression test

Note. Sub-analyses were conducted for those disorders where heterogeneity was found to be present, and as such, ASD was not included.
on the pathognomonic behavioral 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 behaviors are more likely to get referred to a specialized FASD diagnostic clinic than those without such behaviors. Further, clinical populations are likely to be much more severely impaired and have crossed a threshold.

Figure 8. The prevalence of ADHD, ASD, CD and ODD among children with FASD and without FASD (i.e., the general population of the United States)

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

Sources: (Christensen et al., 2016; Costello et al., 2003; Kessler et al., 2005).

Figure 8 shows the prevalence of ADHD, ASD, CD, and ODD among children with FASD and without FASD. The figure illustrates that children with FASD have a significantly higher prevalence of these disorders compared to those without FASD.
where parents or caretakers are seeking help. Thus, relying on clinically-referred samples to
determine the prevalence of neurodevelopmental disorders with prominent externalizing
behaviors 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
(Chasnoff et al., 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,
Payne, Haan, & Bower, 2006; Payne et al., 2005).

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. Further, it must be acknowledged that the mere occurrence of FASD with any other neurodevelopmental disorders (or the presence of any of the defining features of other neurodevelopmental disorders) does not necessarily represent causality. What is clear however, is that this study clearly demonstrates that children with FASD experience some
comorbid neurodevelopmental disorders at rates notably higher than the prevalence in the general population of the United States.
Chapter 4 Identification of a Neurodevelopmental Profile of FASD: FASD versus Typically Developing Control Children

This chapter was modified from the following:

4.1 Introduction

It is well documented that individuals with FASD exhibit a broad array of neurodevelopmental impairments such as deficits in adaptive function, attention, executive function, motor function, social cognition, verbal and nonverbal learning, as well as externalizing behaviors (Kodituwakku, 2009; Mattson et al., 2011). It is also commonly reported that children with FASD have diminished intellectual functioning (Mattson et al., 1997); however, when compared with IQ-matched control children, differences in their neurodevelopmental presentation have been noted (Vaurio, Riley, & Mattson, 2011). Although, it is widely accepted that the neurodevelopmental and behavioral effects of prenatal alcohol exposure are far-reaching (Mattson et al., 2011), the current diagnostic guidelines tend to focus on the severity of the neurodevelopmental impairments rather than the specificity of the impairments.

Early and accurate diagnosis of FASD is crucial to providing timely developmental interventions, which are key to altering the developmental trajectory of affected individuals with respect to social functioning, improving their quality of life, and preventing subsequent adverse outcomes common among individuals with FASD, such as school failure and dropout, addiction, mental health problems, dependent living, as well as involvement with the law and incarceration (Streissguth, Barr, Kogan, & Bookstein, 1996). However, diagnosing FASD is difficult due to the lack of a universal diagnostic approach and widely accepted diagnostic criteria (Chudley, 2018; Coles et al., 2016). The absence of a standardized set of criteria can lead to diagnostic misclassification, the inability to detect a clinically meaningful difference between individuals with FASD and other clinical populations, and inappropriate treatments and interventions (Astley & Clarren, 2000). Furthermore, in clinical settings where FASD is an important area of emphasis, individuals
who have been affected by prenatal alcohol exposure often go undiagnosed or are misdiagnosed (Chasnoff et al., 2015).

In an effort to improve the screening and diagnosis of individuals with FASD, a distinct pathognomonic neurodevelopmental profile of FASD may assist in: i) accurate identification of individuals with FASD, by adding to the resources available to clinicians; ii) discrimination of FASD from other clinical populations (i.e., differential diagnosis); iii) ascertainment of accurate prevalence estimates; iv) planning/development of appropriate targeted interventions for individuals with FASD; v) enhancement of clinical services for this population; and, finally, vii) triaging individuals most in need of a full multidisciplinary FASD diagnostic assessment. As such, the objective of the current study was to identify a neurodevelopmental profile which can differentiate children with FASD from typically developing children.

As discussed above, FASD includes several distinct diagnoses. As such, there is the possibility that individuals with FASD exhibit more than one neurodevelopmental profile (i.e., a unique profile could exist for each diagnostic category). In order to explore this possibility, the current study utilized a methodology that allows for the empirical determination of the number of distinct profiles.

4.2 Methods

4.2.1 Participants

This study consisted of a secondary analysis of data from the Canadian component of the World Health Organization (WHO) International Study on the Prevalence of FASD (World
The Canadian FASD prevalence study used a cross-sectional, observational design using active case ascertainment (an epidemiological surveillance strategy in which cases are actively sought for examination and diagnosis), along with retrospective collection of prenatal alcohol exposure information, to identify cases of suspected FASD among 2,555 elementary school students aged 7-9 years attending public school in the Greater Toronto Area in Ontario, Canada. The study procedures involved two phases of data collection and followed a step-wise approach, where only those children meeting predetermined criteria proceeded to the subsequent phase. Phase I involved: i) taking growth measurements, ii) identifying learning and/or behavioral problems, and iii) a dysmorphology examination. Children were selected to proceed to Phase II if they met one or more of the following criteria:

   a) height and weight at or below the 10th percentile;
   b) occipitofrontal circumference at or below the 10th percentile;
   c) presence of at least two of the three characteristic sentinel facial features that discriminate between individuals with and without FAS:
      i. short palpebral fissures (2 standard deviations below the mean; at or below the 3rd percentile),
      ii. smooth or flattened philtrum (4 or 5 on the 5-point Likert scale of the lip-philtrum guide) (Astley & Clarren, 2000), and
      iii. thin vermilion border of the upper lip (4 or 5 on the 5-point Likert scale of the lip-philtrum guide) (Astley & Clarren, 2000); and
   d) existing learning and/or behavioral problems, neurodevelopmental disorder(s) and/or learning disabilities.

Phase II involved: i) a neurodevelopmental assessment, ii) maternal interview, and iii) behavioral observations/ratings by parents, obtained via the CBCL (Achenbach & Rescorla,
2001). An interview with the biological mother was requested for children who demonstrated deficits (defined as two standard deviations below the mean on a subtest) in a minimum of two domains assessed during the neurodevelopmental assessment. This threshold was set to increase the likelihood that all potential cases were identified, as impairment of a minimum of three domains is necessary for a FASD-specific diagnosis. At the end of the interview, the mother was asked to complete the CBCL.

In addition to those children meeting the specified criteria, a group of typically developing control children was randomly selected from a list of all children who completed Phase I and who did not meet the criteria for Phase II using a systematic sampling technique; these children underwent a complete assessment in Phase II (i.e., neurodevelopmental assessments, maternal interviews to collect prenatal alcohol exposure history, and behavioral observations/ratings), as described above. Students who were subsequently found (based on the maternal interview) to have been prenatally exposed to alcohol or to have a pre-existing neurodevelopmental disorder were excluded from the control group.

Final diagnostic screening conclusions were made, by consensus, by a team of experienced multidisciplinary experts, using the 2005 Canadian diagnostic guidelines (Chudley et al., 2005). The Canadian FASD prevalence study was a screening study where only children who were most in need of a full diagnostic assessment were identified and thus, it is not necessarily the case that diagnoses of all suspected cases would be confirmed following a full multidisciplinary clinical assessment. As such, the term “suspected” FASD is used throughout. A detailed description of the methodology of the Canadian FASD prevalence study is presented in Popova et al. (Popova, Lange, Chudley, Reynolds, & Rehm, 2018)
4.2.2 Measures

4.2.2.1 Neurodevelopmental assessment

Neurodevelopmental assessments were conducted by qualified psychometrists using the WHO International Study on the Prevalence of FASD test battery, which included tests of attention, executive function, general cognition, language, processing speed, sensorimotor working memory and visuospatial processing. The following neurodevelopmental test battery was used:

- The Wechsler Abbreviated Scales of Intelligence, Second Edition (WASI-II) (Wechsler, 2011), which includes the following four subtests:
  - Block design
  - Matrix reasoning
  - Similarities
  - Vocabulary

- The following four subtests from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (Wechsler, 2008):
  - Coding
  - Digit span (forward and backward)
  - Letter-number sequencing
  - Symbol search

- The following four subtests from the NEPSY, Second Edition (NEPSY-II) (Korkman, Kirk, & Kemp, 2007):
  - Arrows
  - Auditory attention and response set
  - Fingertip tapping
This test battery was devised based on the minimum measurements necessary to screen children for FASD. All tests were administered and scored by the examiner according to published test manuals and rechecked by a second examiner. The team of psychometrists were supervised by a registered psychologist. Raw scores were converted to scaled scores according to age and sex norms. Canadian norms were used for the WISC-IV, and US norms were used for the WASI-II and NEPSY-II (as Canadian norms are not available for the respective instruments).

4.2.2.2 Behavioral observations/ratings by parents

Parents were asked to complete the CBCL to evaluate their child’s social competencies and identify any behavioral problems. T-scores were computed for 23 composite scales using 113 behavioral descriptors, scored on a three-point Likert scale (0=absent, 1=occurs sometimes, 2=occurs often), according to age and sex norms.

4.2.3 Latent profile analysis

Latent profile analysis (LPA) (Loehlin, 1998) was conducted to identify latent neurodevelopmental profiles. LPA was performed on a sample of children with suspected FASD and typically developing control children. A step-wise approach was used to select indicator variables for the LPA. A total of 42 variables were available for consideration (22 derived from the subtests of the neurodevelopmental test battery and 20 derived from the composite scales of the CBCL). Variables were initially selected based on standardized differences in means between children with suspected FASD and typically developing
control children (measured through Cohen’s $d$) (Cohen, 1988) variables with a large effect size ($d \geq 0.8$) were retained. Pearson’s correlation coefficients ($r$) were calculated to avoid the inclusion of redundant variables. For strongly correlated variables ($r \leq -0.7$ or $r \geq 0.7$), the variable with the larger effect size was retained. If the effect sizes were equal, Student’s unpaired t-tests were performed (to test differences in the means between children with suspected FASD and typically developing control children), and the variable with the larger t-score was retained.

4.2.3.1 Model selection

To determine the likely number of subgroups present in the sample, based on the observed indicator variables, LPA model fit was tested iteratively based on an increasing number of classes. Determination of the best fitting LPA model was based jointly on the Akaike Information Criterion (AIC) (Akaike, 1974), Bayesian Information Criterion (BIC) (Sclove, 1987), log likelihood and the Lo-Mendell-Rubin adjusted log likelihood ratio test (Lo, Mendell, & Rubin, 2001). Optimal model fit was defined by lower relative AIC and BIC values and higher log likelihood values. Further, an entropy value $>0.8$ was used as an indicator of highly discriminating latent classes (i.e., an indicator of low classification uncertainty) (Celeux & Soromenho, 1996).

4.2.3.2 Model evaluation

In LPA, following the determination of the likely number of classes, participants are subsequently assigned to a subgroup based on the probability of membership as indicated by the model. This assignment allows for the model’s classification function, as a binary classification test, to be evaluated. This evaluation was achieved through the calculation of
the resulting model’s sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity, specificity, PPV and NPV are measures of a binary classification test’s accuracy. Sensitivity is the probability of a positive test result among those with the condition, while specificity is the probability of a negative test result among those without the condition. PPV is the probability that those with a positive test actually have the condition, and NPV is the probability that those with a negative test truly do not have the condition. The 95% CI for each measure of interest was approximated using 10,000 bootstrapped samples (with CIs based on the 2.5th and 97.5th percentiles of the bootstrapped generated estimates). Further, Cohen’s d and unpaired Student’s t-test for normally distributed data were used to compare the resulting subgroups on each of the observed indicator variables.

4.2.4 Post-hoc analysis

High levels of prenatal alcohol exposure have been found to be associated with an increased risk of IQ deficits (Mattson et al., 1997). In order to determine if children with suspected FASD are distinguishable by IQ alone, a LPA was performed using IQ only (obtained using the WISC-IV, FSIQ-4 score).

4.2.5 Missing data imputation

Little’s missing completely at random (MCAR) test (Little, 1988) was performed to test the assumption that missing data were missing completely at random ($X^2(3) = 2.163, p = 0.539$); this was confirmed. As such, missing data were replaced by the mean score of the complete cases in the study sample (i.e., mean imputation). To determine if the mean imputation of missing data had influenced the classification function of the final model, a sensitivity LPA
was performed for only those participants with complete neurodevelopmental and behavioral data, and the resulting model’s sensitivity, specificity, PPV, and NPV were computed.

### 4.2.6 Statistical software

Variable selection and the MCAR test were performed using Stata version 15.1 (Stata Corporation, 2017), the LPA was conducted using Mplus version 8.0 (Muthén & Muthén, 2017), and CIs were computed in R version 3.4.4 (R Core Team, 2016). Statistical significance was based on an acceptable type-I error rate (α) of 0.05.

### 4.3 Results

A total of 21 children with suspected FASD (52.4% male; mean [SD] age: 9.7 [0.8]) and 37 typically developing control children (70.3% male; mean [SD] age: 9.0 [1.0]) were included in the main analysis. The group of children with suspected FASD had the following diagnostic breakdown: three (14.3%) cases of FAS, two (9.5%) cases of pFAS, and 16 (76.2%) cases of ARND. Children with suspected FASD differed from typically developing control children with respect to age ($p = 0.007$), occipitofrontal circumference ≤10th percentile ($p = 0.002$), height ≤10th percentile ($p = 0.011$), right palpebral fissure length 2 standard deviations below the mean ($p = 0.040$), and IQ ($p < 0.001$); they did not differ from typically developing control children on sex, handedness, ethnicity, weight, or the three characteristic facial features that discriminate individuals with and without FAS or pFAS, aside from the right palpebral fissure length. Demographic and descriptive data for study participants are presented in Table 10.
Table 10. Demographic and descriptive characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Children with suspected FASD (n=21)</th>
<th>Typically developing control children (n=37)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – mean (SD)</td>
<td>9.7 (0.8)</td>
<td>9.0 (1.0)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>7.9-11.0</td>
<td>7.2-11.3</td>
</tr>
<tr>
<td>Sex (male) – n (%)</td>
<td>11 (52.4)</td>
<td>26 (70.3)</td>
<td>0.173</td>
</tr>
<tr>
<td>Handedness (right) – n (%)</td>
<td>17 (81.0)</td>
<td>32 (86.5)</td>
<td>0.576</td>
</tr>
<tr>
<td>Ethnicity – n (%)</td>
<td></td>
<td></td>
<td>0.151</td>
</tr>
<tr>
<td>Caucasian</td>
<td>15 (71.4)</td>
<td>16 (43.2)</td>
<td></td>
</tr>
<tr>
<td>African Canadian/Caribbean</td>
<td>1 (4.8)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Eastern European</td>
<td>2 (9.5)</td>
<td>5 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Western European</td>
<td>3 (14.3)</td>
<td>11 (29.7)</td>
<td></td>
</tr>
<tr>
<td>Chinese/South East Asian</td>
<td>0 (0.0)</td>
<td>1 (2.7)</td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>0 (0.0)</td>
<td>4 (10.8)</td>
<td></td>
</tr>
<tr>
<td>IQ&lt;sup&gt;b&lt;/sup&gt; – mean (SD)</td>
<td>87.2 (10.2)</td>
<td>106.4 (12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>71-116</td>
<td>80-138</td>
</tr>
<tr>
<td>Height ≤10&lt;sup&gt;th&lt;/sup&gt; percentile – n (%)</td>
<td>5 (23.8)</td>
<td>1 (2.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Weight ≤10&lt;sup&gt;th&lt;/sup&gt; percentile – n (%)</td>
<td>4 (19.1)</td>
<td>6 (16.2)</td>
<td>0.784</td>
</tr>
<tr>
<td>OFC ≤10&lt;sup&gt;th&lt;/sup&gt; percentile – n (%)</td>
<td>5 (23.8)</td>
<td>0 (0.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Right PFL 2SD below the mean – n (%)</td>
<td>10 (47.6)</td>
<td>8 (21.6)</td>
<td>0.040</td>
</tr>
<tr>
<td>Left PFL 2SD below the mean – n (%)</td>
<td>9 (42.9)</td>
<td>9 (24.3)</td>
<td>0.143</td>
</tr>
<tr>
<td>Smooth philtrum (4 or 5 on the Lip-Philtrum Guide) – n (%)</td>
<td>Children (n=21)</td>
<td>Typically developing control (n=37)</td>
<td>P-value&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>----------------</td>
<td>------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>5 (23.8)</td>
<td>12 (32.4)</td>
<td></td>
<td>0.723</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thin vermillion border (4 or 5 on the Lip-Philtrum Guide) – n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (19.1)</td>
<td>8 (22.2)</td>
<td></td>
<td>0.966</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FASD diagnostic category&lt;sup&gt;c&lt;/sup&gt; – n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>3 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pFAS</td>
<td>2 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARND</td>
<td>16 (76.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OFC: occipitofrontal circumference; PFL: palpebral fissure length; SD: standard deviation

<sup>a</sup>P-values are based on chi-square (for categorical variables) and Student’s unpaired t-test (for continuous variables)

<sup>b</sup>WISC-IV: FSIQ-4

<sup>c</sup>As per the 2005 Canadian diagnostic guidelines (Chudley et al., 2005).
Based on the variable selection process, described above, ten observed indicator variables were retained. Eight variables were derived from the neurodevelopmental test battery (WASI-II – block design, similarities, and vocabulary; WISC-IV – coding and symbol search; and NEPSY-II – response set, arrows, and word generation (letters)); and two variables were derived from the CBCL (attention problems and rule breaking behavior). Based on the model fit statistics, the 2-class model (AIC: 3,159.5, BIC: 3,223.3, log likelihood: -1,548.7, \( p = 0.149 \)) fit better than the 1-class model (AIC: 3,275.2, BIC: 3,316.4, log likelihood: -1,617.6). When compared to the 2-class model, the 3-class model had a lower AIC (3,144.6), but a higher BIC (3,231.1) and log likelihood (-1,530.3, \( p = 0.512 \)). As such, the 2-class model was retained (see Table 11 for the model fit statistics).

<table>
<thead>
<tr>
<th>Table 11. Model fit statistics for the 1-, 2-, and 3-class models tested</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main analysis</strong></td>
</tr>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>AIC</td>
</tr>
<tr>
<td>BIC</td>
</tr>
<tr>
<td>Log likelihood</td>
</tr>
<tr>
<td>P-value*</td>
</tr>
<tr>
<td>Entropy</td>
</tr>
</tbody>
</table>

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; “-”: not applicable

*P-value is in reference to the respective model’s comparison with the lower class solution.
For the 2-class model, 24 participants (41.4% of the sample) were assigned to subgroup 1, and 34 participants (58.6% of the sample) were assigned to subgroup 2. Participants in subgroup 1 performed worse than participants in subgroup 2 for each of the eight observed variables derived from the subtests of the neurodevelopmental test battery and scored higher on the two observed variables derived from the CBCL composite scales (Table 12).

The final 2-class model resulted in 91.4% of participants being classified correctly overall, with almost all (20 out of 21; 95.2% [sensitivity], 95% CI: 84.2%-100.0%) children with suspected FASD assigned to subgroup 1 and significantly more (33 out of 37; 89.2% [specificity], 95% CI: 78.4%-97.5%) typically developing control children assigned to subgroup 2. Among those in subgroup 1, 83.3% (95% CI: 66.7%-96.2%) were children with suspected FASD (PPV), and among those in subgroup 2, 97.1% (95% CI: 90.3%-100.0%) were typically developing control children (NPV). See Table 13 for the number of children with suspected FASD and typically developing control children assigned to each subgroup.

4.3.1 Post-hoc analysis: Latent profile analysis based on IQ only

When LPAs were performed using IQ as the only indicator variable, the 1-class model (AIC: 482.4, BIC: 486.6, log likelihood: -239.2) fit better than the 2-class model (AIC: 483.8, BIC: 492.1, log likelihood: -237.9, p = 0.190). As such, the model with IQ only was not explored further. Although the mean IQs for children with suspected FASD and for typically developing control children were found to be statistically significantly different (87.2 [SD=10.2] vs. 106.4 [SD=12.9], respectively; p<0.001), the post-hoc analysis demonstrated that these two groups of children could not be differentiated based on IQ only.
Table 12. Mean scores (SD) for each subgroup in the 2-class model

<table>
<thead>
<tr>
<th>Observed variable/measure</th>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
<th>d</th>
<th>t-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEURODEVELOPMENTAL TEST BATTERY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WASI-II: block design</td>
<td>8.79</td>
<td>12.32</td>
<td>3.88</td>
<td>1.03</td>
<td>4.135</td>
</tr>
<tr>
<td>WASI-II: similarities</td>
<td>7.79</td>
<td>10.47</td>
<td>3.22</td>
<td>0.99</td>
<td>3.863</td>
</tr>
<tr>
<td>WASI-II: vocabulary</td>
<td>7.96</td>
<td>12.00</td>
<td>3.70</td>
<td>1.16</td>
<td>4.450</td>
</tr>
<tr>
<td>WISC-IV: coding</td>
<td>5.63</td>
<td>10.15</td>
<td>2.35</td>
<td>1.59</td>
<td>5.590</td>
</tr>
<tr>
<td>WISC-IV: symbol search</td>
<td>6.79</td>
<td>11.59</td>
<td>2.58</td>
<td>1.89</td>
<td>7.152</td>
</tr>
<tr>
<td>NEPSY-II: arrows</td>
<td>7.25</td>
<td>11.59</td>
<td>2.45</td>
<td>1.55</td>
<td>5.544</td>
</tr>
<tr>
<td>NEPSY-II: response set</td>
<td>7.13</td>
<td>11.82</td>
<td>2.79</td>
<td>1.52</td>
<td>5.485</td>
</tr>
<tr>
<td>NEPSY-II: word generation (letter)</td>
<td>8.08</td>
<td>10.37</td>
<td>2.63</td>
<td>0.79</td>
<td>2.861</td>
</tr>
</tbody>
</table>

CHILD BEHAVIOR CHECKLIST

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention problems</td>
<td>60.73</td>
<td>8.08</td>
<td>51.53</td>
<td>2.30</td>
</tr>
<tr>
<td>Rule breaking behavior</td>
<td>56.08</td>
<td>6.67</td>
<td>51.88</td>
<td>2.96</td>
</tr>
</tbody>
</table>

d: Cohen’s d; SD: standard deviation

Note. Subgroup 1 is comprised of 20 children with suspected FASD and four typically developing control children. Subgroup 2 is comprised of one child with suspected FASD and 33 typically developing control children.
4.3.2 Sensitivity analysis

Nineteen (out of 21) children with suspected FASD and 36 (out of 37) typically developing control children had complete neurodevelopmental and behavioral data, and thus, were included in the sensitivity analysis. As in the main analysis, the 2-class model was retained based on the model fit statistics (see Table 11). The final 2-class model classified 89.1% of participants correctly overall and had a sensitivity of 94.7% (95% CI: 82.4%-100.0%), specificity of 86.1% (95% CI: 74.2%-97.0%), PPV of 78.3% (95% CI: 60.0%-94.7%), and NPV of 96.9% (95% CI: 90.0%-100.0%; see Table 13). As such, the mean imputation of missing data had little influence on the classification function of the final 2-class model.

4.4 Discussion

The neurodevelopmental profile of FASD identified in the current study was successful in discriminating children with suspected FASD from typically developing control children with a sensitivity of 95.2% and specificity of 89.2%, and thus, from a clinical perspective, these neurodevelopmental profiles may have a high psychometric utility. The identified neurodevelopmental profile of FASD, which consists of impairments in perceptual reasoning, verbal comprehension, visual-motor speed and motor coordination, processing speed (nonverbal information), attention and executive function, visuospatial processing, and language, in combination with rule-breaking behavior and attention problems, was more accurate at identifying children with suspected FASD than was IQ alone. This finding supports the notion that the neurodevelopmental impairments of individuals with FASD are more specific than a general cognitive impairment (Mattson et al., 2011; Mattson et al., 2010).
Table 13. Number of children assigned to each subgroup and the classification function of the 2-class model for the main and sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>Main analysis</th>
<th>Sensitivity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suspected FASD (n)</td>
<td>Typically developing control children (n)</td>
</tr>
<tr>
<td>Subgroup 1</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Subgroup 2</td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

Classification function

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>95.2</td>
<td>89.2</td>
<td>83.3</td>
<td>97.1</td>
</tr>
<tr>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.7</td>
<td>86.1</td>
<td>78.3</td>
<td>96.9</td>
</tr>
<tr>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
</tr>
<tr>
<td>PPV</td>
<td>94.7</td>
<td>86.1</td>
<td>78.3</td>
<td>96.9</td>
</tr>
<tr>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
</tr>
<tr>
<td>NPV</td>
<td>94.7</td>
<td>86.1</td>
<td>78.3</td>
<td>96.9</td>
</tr>
<tr>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
<td>(95% CI: 84.2-100.0)</td>
</tr>
</tbody>
</table>

FASD: Fetal Alcohol Spectrum Disorder; NPV: negative predictive value; PPV: positive predictive value

The current study is the first to identify a neurodevelopmental profile of FASD among a population-based sample of children with suspected FASD – the sample was drawn from a cross-sectional, population-based study that utilized active case ascertainment (the gold standard) (May & Gossage, 2001) to identify cases of suspected FASD. This is also the first study to analyze and incorporate both behavioral observations/ratings of parents and performance-based measures of neurodevelopment when seeking to identify a neurodevelopmental profile of FASD.
The finding that children with FASD can be accurately distinguished from typically developing control children using standard measures of the neurodevelopmental effects of prenatal alcohol exposure are in line with a previous clinical study by Mattson and colleagues (Mattson et al., 2010). In 2010, Mattson and colleagues (Mattson et al., 2010) sought to identify a neurodevelopmental profile of FASD using 22 variables derived from the subtests of a battery of standardized tests – their approach to variable selection was similar to that of the current study. When comparing individuals (7 to 21 years of age) prenatally exposed to alcohol who met the study criteria for FAS (n=41) with individuals prenatally unexposed to alcohol (n=46), their profile had a sensitivity of 88% and specificity of 96%. In a subsequent study (Mattson et al., 2013), these investigators attempted to refine their initial neurodevelopmental profile by reducing the included number of variables to 11, selected solely on clinical judgement, which resulted in a profile with a notably lower sensitivity (77%) and specificity (76%). Although Mattson and colleagues were able to demonstrate that a set of neurodevelopmental measures could potentially be used to delineate individuals with FASD from unexposed individuals, they relied on clinic-based samples, which are prone to sampling bias, and thus, ultimately undermined the external validity of the findings. Further, the classification of individuals as having FAS was not reflective of how FAS is classified elsewhere, limiting the applicability of the profiles.

As would be expected with a population-based sample (Chudley, 2008), the group of children with suspected FASD in the current study consisted mainly of children with suspected ARND (76.2%). Given that the diagnosis of ARND is based solely on evidence of brain dysfunction, as the characteristic facial features and growth deficits present with FAS and pFAS are often absent with ARND, identifying a profile that successfully identifies children with ARND is clinically advantageous.
Given the methodology of the Canadian component of the WHO International Study on the Prevalence of FASD (World Health Organization, n.d.), there are a few limitations of the current study. First, the cases of suspected FASD identified in the Canadian FASD prevalence study may not be representative of the FASD population in terms of the levels of severity because of the potential of self-selection bias (i.e., the parents’ decision to allow their child to participate in the study may reflect some inherent bias in the characteristics of their child). Second, the neurodevelopmental test battery was predetermined for the purposes of the WHO International Study on the Prevalence of FASD, and thus, it may not include the measurement of some brain domains that could be particularly useful in the identification of a unique neurodevelopmental profile of FASD. Third, the overall sample size was relatively small.

Within the current FASD diagnostic framework (Chudley et al., 2005; Hoyme et al., 2016) the neurodevelopmental profile of FASD identified in the current study has the potential to be used as a screening tool for triaging children most in need of a full multidisciplinary diagnostic assessment, as it was successful in discriminating children with suspected FASD from typically developing control children. The current neurodevelopmental profile was derived from eight quick and relatively easy to administer neurodevelopmental subtests, as well as from two composite scores of the CBCL (based on a total of 27 behavioral descriptors). However, its full clinical utility can only be determined following additional research. First, it remains to be determined whether the profile is able to differentiate children with FASD from other clinical populations (e.g., children with Attention-Deficit Hyperactivity Disorder) or whether the identified neurodevelopmental profile is specific to the effects of prenatal alcohol exposure. Second, the cross-cultural utility of the identified neurodevelopmental profile needs to be explored. Third, the profile should be tested on a
sample of adolescents and adults with FASD to determine its usefulness among older individuals.
Chapter 5 Exploring the Uniqueness of the Identified Neurodevelopmental Profile of FASD

This chapter was modified from the following:

Lange, S., Shield, K., Popova, S., Anagnostou, E., & Rehm, J. (Submitted). Fetal alcohol spectrum disorder: Neurodevelopmentally and behaviorally indistinguishable from other neurodevelopmental disorders. *Child Development.*
5.1 Introduction

Considering the wide range of neurodevelopmental impairments associated with FASD and the adverse developmental trajectory common to affected individuals, it is important to identify children who may be affected by prenatal alcohol exposure as early as possible, as early diagnosis and the implementation of early developmental interventions can alleviate subsequent adverse outcomes (Streissguth et al., 2004). However, diagnosing FASD is difficult for a number of reasons namely, the high rate of comorbidity (Lange, Rehm, Anagnostou, & Popova, 2018; Popova et al., 2016), and the overlapping signs and symptoms with other neurodevelopmental disorders (McLennan, 2015). Accordingly, FASD is often misdiagnosed (Chasnoff et al., 2015), which has a number of consequences, specifically implications for treatment, inaccurate incidence and prevalence estimates and reduced power to detect a clinically meaningful difference between groups in clinical research studies (Astley & Clarren, 2000; Chasnoff et al., 2015).

Given the consequences of misdiagnosis (Astley & Clarren, 2000; Chasnoff et al., 2015), attention has been given to the identification of a distinct neurodevelopmental profile to aid in the accurate identification of children with FASD and the discrimination of FASD from idiopathic neurodevelopmental disorders (Lange, Shield, Rehm, Anagnostou, & Popova, Submitted; Mattson et al., 2010; Mattson et al., 2013). The current study is intended to build on the work of Lange and colleagues (Lange et al., Submitted), who identified a neurodevelopmental profile that was successful in discriminating children with suspected FASD from typically developing control children with 95.2% sensitivity and 89.2% specificity (see Chapter 4). In order to determine the identified profile’s full clinical utility, its ability to differentiate children with FASD from children with other neurodevelopmental disorders must be tested. As such, the objective of the current study was to test whether the identified
neurodevelopmental profile of FASD is unique and able to differentiate children with suspected FASD from children with other neurodevelopmental disorders – i.e., whether the neurodevelopmental profile is specific to children with FASD.

5.2 Methods

5.2.1 Participants

This study consisted of a secondary analysis of data from the Canadian component of the WHO International Study on the Prevalence of FASD (World Health Organization, n.d.). The Canadian FASD prevalence study used a cross-sectional, observational design using active case ascertainment, along with retrospective collection of prenatal alcohol exposure information, to identify cases of suspected FASD among 2,555 elementary school students aged 7-9 years attending public school in the Greater Toronto Area in Ontario, Canada (Popova, Lange, Chudley, Reynolds, & Rehm, 2018). As in the study by Lange and colleagues (Lange et al., Submitted) the term “suspected” FASD is used throughout, as the Canadian FASD prevalence study was a screening study in which all children who were suspected to have FASD were referred for a full multidisciplinary clinical assessment.

The Canadian FASD prevalence study procedures involved two phases of data collection and followed a step-wise approach, where only those children meeting predetermined criteria proceeded to the subsequent phase. Phase I involved: i) taking growth measurements, ii) identifying learning and/or behavioral problems, and iii) a dysmorphology examination. Phase II involved: i) a neurodevelopmental assessment, ii) maternal interview, and iii) behavioral observations/ratings by parents, obtained via the CBCL (Achenbach & Rescorla, 2001).
In addition to those children meeting the specified criteria, a group of typically developing control children was randomly selected from a list of all children who completed Phase I and who did not meet the criteria for Phase II using a systematic sampling technique; these children underwent a complete assessment in Phase II. See Chapter 4, Section 4.2.1 Participants for the criteria used to select children to proceed to Phase II. Final FASD diagnostic screening conclusions were made, by consensus, by a team of experienced multidisciplinary experts, using the 2005 Canadian diagnostic guidelines (Chudley et al., 2005).

As part of the identification of learning and/or behavioral problems in Phase I, children with a pre-existing diagnosis of a neurodevelopmental disorder were identified by their teacher and/or parents/guardians. In cases where the diagnosis was relayed to the research team by the teacher, it was subsequently confirmed with the parents/guardians. The biological mothers of all children identified with a pre-existing neurodevelopmental disorder were invited for an interview to screen for prenatal alcohol use. For the purpose of the current study, children identified to have an existing neurodevelopmental disorder were limited to those with ADHD and/or ASD, as there were too few children who had other neurodevelopmental disorders to make meaningful comparisons. Further, only those children whose mothers were interviewed and prenatal alcohol use was reported to be minimal (less than 1 drink per week on average, and no more than 2 drinks on a single occasion) were included in the current study.

5.2.2 Neurodevelopmental profile

The neurodevelopmental profile identified by Lange and colleagues (Lange et al., Submitted) was derived from the WHO International Study on the Prevalence of FASD
neurodevelopmental test battery, which was administered by qualified psychometrists. The profile consisted of ten observed indicator variables.

- Eight indicator variables were derived from the neurodevelopmental test battery:
  - WASI-II (Wechsler, 2011) – Block design, similarities, and vocabulary;
  - WISC-IV (Wechsler, 2008) – Coding and symbol search; and
  - NEPSY-II (Korkman et al., 2007) – Arrows, response set, and word generation (letters).
- Two variables were derived from the CBCL (Achenbach & Rescorla, 2001):
  - Attention problems; and
  - Rule breaking behavior.

For additional details on the full test battery from which the respective profile was derived, the methods of selecting variables to be included, as well as methods of administration and scoring, see Chapter 4, Section 4.2.2.1 Neurodevelopmental assessment and Lange et al. (Lange et al., Submitted).

5.2.2 Statistical analysis

As part of the descriptive statistics, groups of participants (children with suspected FASD, children with other neurodevelopmental disorders [ADHD and/or ASD] and typically developing control children) were compared with respect to demographics, growth and dysmorphology characteristics, as well as IQ. Chi-square was used for analysis of categorical variables. For continuous variables, one-way analysis of variance (ANOVA) was used. With a statistically significant ANOVA, post-hoc analyses using Tukey’s pairwise comparisons of means with equal variance were performed. Children with ADHD and/or
ASD were combined for statistical reasons (i.e., there were too few children with ASD for them in their own separate group), and not because they were assumed to be a homogeneous group with respect to their neurodevelopment.

5.2.2.1 Missing data imputation

Little’s MCAR test (Little, 1988) was performed to test the assumption that missing data were missing completely at random ($X^2(3) = 2.575, p = 0.462$); this was confirmed. As such, missing data were replaced by the mean score of the complete cases of the respective group of participants (i.e., mean imputation).

5.2.2.2 Latent profile analysis

LPA (Loehlin, 1998) was conducted using the ten observed indicator variables specified above. LPA was performed on a sample of children with suspected FASD, ADHD and/or ASD, as well as typically developing control children. To determine the likely number of subgroups present in the sample, based on the observed indicator variables, LPA model fit was tested iteratively based on an increasing number of classes. Determination of the best fitting LPA model was based jointly on the AIC (Akaike, 1974), BIC (Sclove, 1987), log likelihood, and the Lo-Mendell-Rubin adjusted log likelihood ratio test (Lo et al., 2001). Optimal model fit was defined by lower relative AIC and BIC values and higher log likelihood values. Further, an entropy value $>0.8$ was used as an indicator of highly discriminating latent classes (i.e., an indicator of low classification uncertainty) (Celeux & Soromenho, 1996).
5.2.2.2.1 Model evaluation

In LPA, following the determination of the likely number of classes, participants are subsequently assigned to a subgroup based on the probability of membership as indicated by the model. This assignment allows for the model’s classification function, as a binary classification test, to be evaluated. Sensitivity, specificity, PPV and NPV were evaluated for following comparisons: i) children with suspected FASD vs. children with other neurodevelopmental disorders and typically developing control children, and ii) children with suspected FASD and children with other neurodevelopmental disorders vs. typically developing control children. The 95% CI for each measure of interest was approximated using 10,000 bootstrapped samples (with CIs based on the 2.5th and 97.5th percentiles of the bootstrapped generated estimates). Given the objective of the current study, specificity and NPV are of particular interest. Further, Cohen’s \( d \) and unpaired Student’s t-test for normally distributed data were used to compare the resulting subgroups on each of the observed indicator variables.

5.2.2.3 Sensitivity analysis

Given that the sample consisted of four diagnostically distinct groups (i.e., children with suspected FASD, ADHD and/or ASD, as well as typically developing control children) it was decided a priori that a 4-class model would be explored in addition to the class solution selected based on the model fit statistics. The resulting model’s sensitivity, specificity, PPV, and NPV were calculated, and the 95% CI was approximated using the method specified above. One-way ANOVA was used to compare the resulting subgroups on each of the observed indicator variables. Post-hoc analyses using Tukey’s pairwise comparisons of means with equal variance were performed for each statistically significant ANOVA.
In addition to the group categorization and comparisons made in the main analysis, the children assigned to each subgroup was also explored for: i) children with suspected FASD only, ii) children with ADHD only, iii) children with ASD only, iv) children with comorbid disorders and v) typically developing control children. Sensitivity, specificity, PPV and NPV were then evaluated for following comparisons: i) children with suspected FASD only vs. typically developing control children and children with ADHD only, ASD only and comorbid disorders.

5.2.2.4 Statistical software

Descriptive statistics and the MCAR test were performed using Stata version 15.1 (Stata Corporation, 2017), the LPA was conducted using Mplus version 8.0 (Muthén & Muthén, 2017), and the CIs and all post hoc statistics were computed in R version 3.4.4 (R Core Team, 2016). Statistical significance was based on an acceptable type-I error rate ($\alpha$) of 0.05.

5.3 Results

Data for a total of 86 participants were included in the current study – 21 children with suspected FASD (52.4% male; mean [SD] age: 9.7 [0.8]), 28 children with other neurodevelopmental disorders (75.0% male; mean [SD] age: 9.3 [1.0]), and 37 typically developing control children (70.3% male; mean [SD] age: 9.0 [1.0]). The group of children with suspected FASD had the following diagnostic breakdown: three (14.3%) cases of FAS, two (9.5%) cases of pFAS, and 16 (76.2%) cases of ARND; five of the children with suspected FASD had a pre-existing diagnosis of ADHD (23.8%) and three had a pre-
existing diagnosis of ASD (14.3%). Twenty-three (82.1%) children in the group with other neurodevelopmental disorders had a pre-existing diagnosis of ADHD and 6 (21.4%) had a pre-existing diagnosis of ASD. Comorbid disorders in the group of children with other neurodevelopmental disorders included the following ODD, Reactive Attachment Disorder and Temper Dysregulation Disorder.

The three groups of children differed from one another with respect to ethnicity ($p = 0.020$), height $\leq 10^{th}$ percentile ($p = 0.041$), and occipitofrontal circumference $\leq 10^{th}$ percentile ($p = 0.011$). With regards to mean IQ, both children with suspected FASD (mean = 87.2 [SD = 10.2]) and children with other neurodevelopmental disorders (mean = 95.6 [SD = 14.1]) differed from typically developing control children (mean = 106.4 [SD = 12.9]; $p < 0.001$ and $p = 0.003$, respectively), but were not significantly different from one another ($p = 0.064$). The groups did not significantly differ from one another on age, sex, handedness, weight $\leq 10^{th}$ percentile, or the three characteristic facial features that discriminate individuals with and without FAS or pFAS (i.e., palpebral fissure length 2 standard deviations below the mean, smooth philtrum, and thin vermilion border). Demographic and descriptive data for study participants are presented in Table 14.

Based on the model fit statistics, the 2-class model (AIC: 4,693.5, BIC: 4,769.6, log likelihood: -2,315.8, $p = 0.002$) fit better than the 1-class model (AIC: 4,850.1, BIC: 4,899.2, log likelihood: -2,405.1). Although the 3-class model had a lower AIC (4,665.2) and BIC (4,768.3), and higher log likelihood (-2,290.6, $p = 0.265$), the log-likelihood ratio test was not significant – indicating that the 2-class model was the best fit (see Table 15 for the model fit statistics).
<table>
<thead>
<tr>
<th></th>
<th>Typically developing control children (n=37)</th>
<th>Children with suspected FASD (n=21)</th>
<th>Children with other neurodevelopmental disorders (n=28)</th>
<th>Statistical test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – mean (SD)</td>
<td>9.0 (1.0)</td>
<td>9.7 (0.8)</td>
<td>9.3 (1.0)</td>
<td>F = 3.63</td>
<td>0.505</td>
</tr>
<tr>
<td></td>
<td>7.2-11.3</td>
<td>7.9-11.0</td>
<td>7.3-10.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male) – n (%)</td>
<td>26 (70.3)</td>
<td>11 (52.4)</td>
<td>21 (75.0)</td>
<td>X = 3.03</td>
<td>0.220</td>
</tr>
<tr>
<td></td>
<td>32 (86.5)</td>
<td>17 (81.0)</td>
<td>28 (100.0)</td>
<td>X = 5.29</td>
<td>0.071</td>
</tr>
<tr>
<td>Handedness (right) – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>16 (43.2)</td>
<td>15 (71.4)</td>
<td>13 (46.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African Canadian/Caribbean</td>
<td></td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern European</td>
<td>5 (13.5)</td>
<td>2 (9.5)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western European</td>
<td>11 (29.7)</td>
<td>3 (14.3)</td>
<td>2 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese/South East Asian</td>
<td></td>
<td>1 (2.7)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian/Other</td>
<td>4 (10.8)</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typically developing children (n=37)</td>
<td>Children with suspected FASD (n=21)</td>
<td>Children with other neurodevelopmental disorders (n=28)</td>
<td>Statistical test</td>
<td>(P)-value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IQ(^a) – mean (SD)</td>
<td>106.4 (12.9)</td>
<td>87.2 (10.2)</td>
<td>95.6 (14.1)</td>
<td>(F = 16.18)</td>
<td>(&lt;0.01^{b,c})</td>
</tr>
<tr>
<td>Range</td>
<td>80-138</td>
<td>71-116</td>
<td>63-120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height ≤10(^{th}) percentile – n (%)</td>
<td>1 (2.7)</td>
<td>5 (23.8)</td>
<td>3 (10.7)</td>
<td>(X = 6.37)</td>
<td>0.041</td>
</tr>
<tr>
<td>Weight ≤10(^{th}) percentile – n (%)</td>
<td>6 (16.2)</td>
<td>4 (19.1)</td>
<td>4 (14.3)</td>
<td>(X = 0.20)</td>
<td>0.905</td>
</tr>
<tr>
<td>OFC ≤10(^{th}) percentile – n (%)</td>
<td>0 (0.0)</td>
<td>5 (23.8)</td>
<td>5 (17.9)</td>
<td>(X = 8.96)</td>
<td>0.011</td>
</tr>
<tr>
<td>Right PFL 2SD below the mean – n (%)</td>
<td>8 (21.6)</td>
<td>10 (47.6)</td>
<td>11 (39.3)</td>
<td>(X = 4.63)</td>
<td>0.099</td>
</tr>
<tr>
<td>Left PFL 2SD below the mean – n (%)</td>
<td>9 (24.3)</td>
<td>9 (42.9)</td>
<td>9 (32.1)</td>
<td>(X = 2.15)</td>
<td>0.342</td>
</tr>
<tr>
<td>Smooth philtrum (4 or 5 on the Lip-Philtrum Guide) – n (%)</td>
<td>12 (32.4)</td>
<td>5 (23.8)</td>
<td>9 (32.1)</td>
<td>(X = 4.78)</td>
<td>0.572</td>
</tr>
<tr>
<td>Thin vermilion border (4 or 5 on the Lip-Philtrum Guide) – n (%)</td>
<td>8 (22.2)</td>
<td>4 (19.1)</td>
<td>3 (10.7)</td>
<td>(X = 3.77)</td>
<td>0.708</td>
</tr>
<tr>
<td>FASD diagnostic category(^d) – n (%)</td>
<td></td>
<td></td>
<td>3 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical test</td>
<td>Typically developing control children (n=37)</td>
<td>Children with suspected FASD (n=21)</td>
<td>Children with other neurodevelopmental disorders (n=28)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>pFAS</td>
<td>2 (9.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARND</td>
<td>16 (76.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other neurodevelopmental disorders*—n (%)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Typically Developing Control Children (n=37)</th>
<th>Children with Suspected FASD (n=21)</th>
<th>Children with Other Neurodevelopmental Disorders (n=28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>5 (23.8)</td>
<td>23 (82.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>3 (14.3)</td>
<td>6 (21.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD: attention deficit hyperactivity disorder; ARND: alcohol-related neurodevelopmental disorder; ASD: autism spectrum disorder; FAS: fetal alcohol syndrome; FASD: fetal alcohol spectrum disorder; OFC: occipitofrontal circumference; pFAS: partial fetal alcohol syndrome; PFL: palpebral fissure length; SD: standard deviation.

*WISC-IV: FSIQ-4. **Suspected FASD vs. typically developing control children. ***Children with other neurodevelopmental disorders vs. typically developing control children. ****As per the 2005 Canadian diagnostic guidelines (Chudley et al., 2005). *****Not mutually exclusive.
Table 15. Model fit statistics for the 1-, 2-, 3-, 4-, and 5-class models tested

<table>
<thead>
<tr>
<th></th>
<th>1-class</th>
<th>2-class</th>
<th>3-class</th>
<th>4-class</th>
<th>5-class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIC</strong></td>
<td>4,850.13</td>
<td>4,693.50</td>
<td>4,665.17</td>
<td>4,635.78</td>
<td>4,619.97</td>
</tr>
<tr>
<td><strong>BIC</strong></td>
<td>4,899.22</td>
<td>4,769.58</td>
<td>4,768.25</td>
<td>4,765.86</td>
<td>4,777.05</td>
</tr>
<tr>
<td><strong>Log likelihood</strong></td>
<td>-2,405.07</td>
<td>-2,315.75</td>
<td>-2,290.58</td>
<td>-2,264.89</td>
<td>-2,245.99</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>-</td>
<td>0.002</td>
<td>0.265</td>
<td>0.422</td>
<td>0.373</td>
</tr>
<tr>
<td><strong>Entropy</strong></td>
<td>-</td>
<td>0.894</td>
<td>0.924</td>
<td>0.924</td>
<td>0.931</td>
</tr>
</tbody>
</table>

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; “-”: not applicable

*P-value is in reference to the respective model’s comparison with the lower class solution.

For the 2-class model, 48 participants (55.8% of the sample) were assigned to subgroup 1, and 38 participants (44.2% of the sample) were assigned to subgroup 2. Participants in subgroup 1 performed worse than participants in subgroup 2 for each of the above eight observed variables derived from the subtests of the neurodevelopmental test battery and scored higher on the above two observed variables derived from the composite scales of the CBCL (see Table 16 and Figure 9).

The 2-class model resulted in almost all children with suspected FASD (20 out of 21; 95.2%) and considerably more children with other neurodevelopmental disorders (22 out of 28; 78.6%) being assigned to subgroup 1, and significantly more typically developing control children (31 out of 37; 83.8%) being assigned to subgroup 2 (see Table 17). When comparing children with suspected FASD with typically developing control children and children with other neurodevelopmental disorders, the 2-class model resulted in a specificity of 56.9% (95% CI: 45.1%-69.2%) and NPV of 97.4% (95% CI: 91.4%-100.0%). When
Table 16. Mean scores (SD) for each subgroup in the 2-class model (main analysis)

<table>
<thead>
<tr>
<th>Observed variable/measure</th>
<th>Subgroup 1 Mean</th>
<th>Subgroup 1 SD</th>
<th>Subgroup 2 Mean</th>
<th>Subgroup 2 SD</th>
<th>d</th>
<th>t-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEURODEVELOPMENTAL TEST BATTERY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WASI-II: block design</td>
<td>9.17</td>
<td>2.79</td>
<td>12.63</td>
<td>3.71</td>
<td>1.07</td>
<td>4.785</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WASI-II: similarities</td>
<td>8.08</td>
<td>2.35</td>
<td>10.63</td>
<td>3.09</td>
<td>0.94</td>
<td>4.212</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WASI-II: vocabulary</td>
<td>8.27</td>
<td>3.01</td>
<td>12.11</td>
<td>3.55</td>
<td>1.18</td>
<td>5.311</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WISC-IV: coding</td>
<td>5.75</td>
<td>3.08</td>
<td>10.58</td>
<td>2.15</td>
<td>1.78</td>
<td>8.549</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WISC-IV: symbol search</td>
<td>7.08</td>
<td>2.41</td>
<td>11.68</td>
<td>2.64</td>
<td>1.83</td>
<td>8.331</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NEPSY-II: arrows</td>
<td>7.75</td>
<td>3.31</td>
<td>11.87</td>
<td>2.03</td>
<td>1.46</td>
<td>7.098</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NEPSY-II: response set</td>
<td>7.91</td>
<td>3.29</td>
<td>12.03</td>
<td>2.87</td>
<td>1.32</td>
<td>6.191</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NEPSY-II: word generation (letter)</td>
<td>8.29</td>
<td>2.94</td>
<td>10.72</td>
<td>2.52</td>
<td>0.88</td>
<td>4.127</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CHILD BEHAVIOR CHECKLIST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention problems</td>
<td>62.38</td>
<td>8.22</td>
<td>53.13</td>
<td>5.16</td>
<td>1.32</td>
<td>6.374</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rule breaking behavior</td>
<td>56.50</td>
<td>7.19</td>
<td>52.76</td>
<td>4.03</td>
<td>0.62</td>
<td>3.042</td>
<td>0.003</td>
</tr>
</tbody>
</table>

d: Cohen’s d; SD: standard deviation

Note. Subgroup 1 is comprised of 20 children with suspected FASD, 22 children with other neurodevelopmental disorders, and six typically developing control children. Subgroup 2 is comprised of one child with suspected FASD, six children with other neurodevelopmental disorders, and 31 typically developing control children.
Figure 9. Mean scores for each subgroup in the 2-class model (main analysis)

Note. All scores are presented as z-scores.
Figure 10. Mean scores for each subgroup in the 4-class model (sensitivity analysis)

Note. All scores are presented as z-scores.
Table 17. Number of children assigned to each subgroup in the 2- (main analysis) and 4-class (sensitivity analysis) models

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Main analysis (2-class model)</th>
<th>Sensitivity analysis (4-class model)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suspected FASD (n)</td>
<td>Other neurodevelopmental disorders (n)</td>
</tr>
<tr>
<td>Subgroup 1</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Subgroup 2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Subgroup 3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subgroup 4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>28</td>
</tr>
</tbody>
</table>

FASD: Fetal Alcohol Spectrum Disorder
Table 18. Classification function of the 2- (main analysis) and 4-class (sensitivity analysis) models

<table>
<thead>
<tr>
<th>Classification function (%)</th>
<th>Main analysis (2-class model)</th>
<th>Sensitivity analysis (4-class model)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FASD vs. Typically developing controls and Other neurodevelopmental disorders</td>
<td>FASD vs. Typically developing controls and Other disorders vs. Typically neurodevelopmental disorders</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>95.2 (95% CI: 82.6-100.0)</td>
<td>85.7 (95% CI: 73.5-95.5)</td>
</tr>
<tr>
<td>Specificity</td>
<td>56.9 (95% CI: 45.1-69.2)</td>
<td>83.8 (95% CI: 71.0-94.3)</td>
</tr>
<tr>
<td>PPV</td>
<td>41.7 (95% CI: 28.2-55.3)</td>
<td>87.5 (95% CI: 78.2-95.7)</td>
</tr>
<tr>
<td>NPV</td>
<td>97.4 (95% CI: 91.4-100.0)</td>
<td>81.6 (95% CI: 68.4-94.6)</td>
</tr>
</tbody>
</table>

FASD: Fetal Alcohol Spectrum Disorder; n/a: not applicable; NPV: negative predictive value; PPV: positive predictive value

*a* Assuming subgroup 1 is reflective of the neurodevelopmental profile of FASD and subgroup 2 is reflective of typically developing control children and children with other neurodevelopmental disorders.

*b* Assuming subgroup 1 is reflective of the neurodevelopmental profile of FASD and children with other neurodevelopmental disorders and subgroup 2 is reflective of typically developing control children.

*c* Assuming subgroup 1, 2 and 4 are reflective of the neurodevelopmental profile of FASD and subgroup 3 is reflective of typically developing control children and children with other neurodevelopmental disorders.
dAssuming subgroup 1, 2 and 4 are reflective of the neurodevelopmental profile of FASD and children with other neurodevelopmental disorders and subgroup 2 is reflective of typically developing control children.
comparing children with suspected FASD and children with other neurodevelopmental disorders with typically developing control children, the 2-class model resulted in a specificity of 83.8% (95% CI: 71.0%-94.3%) and NPV of 81.6% (95% CI: 68.4%-94.6%). See Table 18 for classification function of the 2-class model.

5.3.1 Sensitivity analysis

The 4-class model was found to fit better than both a 3-class and a 5-class model (see Table 15). In the 4-class model, 34 participants (39.5% of the sample) were assigned to subgroup 1, nine participants (10.5% of the sample) were assigned to subgroup 2, 36 participants (41.9% of the sample) were assigned to subgroup 3, and seven participants (8.1%) were assigned to subgroup 4. With respect to the eight observed variables derived from the subtests of the neurodevelopmental test battery, participants in subgroup 2 performed the worst, while participants in subgroup 3 performed the best. With respect to the two observed variables derived from the composite scales of the CBCL, participants in subgroup 4 had the highest scores, while participants in subgroup 3 had the lowest scores (see Table 19 and Figure 10).

The 4-class model resulted in all of the children with suspected FASD and most children with other neurodevelopmental disorders (23 out of 28; 82.1%) being assigned to subgroup 1, 2, or 4 (with 61.9% of children with suspected FASD and 53.6% of children with other neurodevelopmental disorders being assigned to subgroup 1), and the majority of typically developing control children (31 out of 37; 83.8%) being assigned to subgroup 3 (see Table 17). When comparing children with suspected FASD with typically developing control children and children with other neurodevelopmental disorders, the 4-class model resulted...
Table 19. Mean scores (SD) for each subgroup in the 4-class model (sensitivity analysis)

<table>
<thead>
<tr>
<th>Observed variable/measure</th>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
<th>Subgroup 3</th>
<th>Subgroup 4</th>
<th>F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>NEURODEVELOPMENTAL TEST BATTERY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WASI-II: block design</td>
<td>9.41</td>
<td>2.49</td>
<td>7.67</td>
<td>3.00</td>
<td>12.78</td>
<td>3.76</td>
</tr>
<tr>
<td>WASI-II: similarities</td>
<td>8.68</td>
<td>2.13</td>
<td>6.11</td>
<td>2.76</td>
<td>10.81</td>
<td>3.02</td>
</tr>
<tr>
<td>WASI-II: vocabulary</td>
<td>9.18</td>
<td>3.05</td>
<td>5.89</td>
<td>2.09</td>
<td>12.17</td>
<td>3.44</td>
</tr>
<tr>
<td>WISC-IV: coding</td>
<td>6.74</td>
<td>2.96</td>
<td>2.33</td>
<td>1.66</td>
<td>10.53</td>
<td>2.20</td>
</tr>
<tr>
<td>WISC-IV: symbol search</td>
<td>7.68</td>
<td>2.18</td>
<td>4.89</td>
<td>2.20</td>
<td>11.81</td>
<td>2.59</td>
</tr>
<tr>
<td>NEPSY-II: arrows</td>
<td>8.82</td>
<td>2.19</td>
<td>3.67</td>
<td>3.50</td>
<td>11.89</td>
<td>2.08</td>
</tr>
<tr>
<td>NEPSY-II: response set</td>
<td>8.68</td>
<td>2.65</td>
<td>4.39</td>
<td>3.82</td>
<td>12.14</td>
<td>2.91</td>
</tr>
<tr>
<td>NEPSY-II: word generation</td>
<td>7.76</td>
<td>2.75</td>
<td>7.22</td>
<td>1.56</td>
<td>10.93</td>
<td>2.38</td>
</tr>
<tr>
<td>(letter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHILD BEHAVIOR CHECKLIST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention problems</td>
<td>60.05</td>
<td>7.26</td>
<td>63.97</td>
<td>8.15</td>
<td>52.69</td>
<td>4.73</td>
</tr>
<tr>
<td>Rule breaking behavior</td>
<td>53.63</td>
<td>4.51</td>
<td>56.82</td>
<td>4.62</td>
<td>52.64</td>
<td>3.93</td>
</tr>
</tbody>
</table>

SD: standard deviation

<sup>a</sup>Subgroup 1 vs. Subgroup 2; <sup>b</sup>Subgroup 1 vs. Subgroup 3; <sup>c</sup>Subgroup 1 vs. Subgroup 4; <sup>d</sup>Subgroup 2 vs. Subgroup 3; <sup>e</sup>Subgroup
2 vs. Subgroup 4; Subgroup 3 vs. Subgroup 4

*Note.* Subgroup 1 is comprised of 13 children with suspected FASD, 15 children with other neurodevelopmental disorders, and six typically developing control children. Subgroup 2 is comprised of five children with suspected FASD and four children with other neurodevelopmental disorders. Subgroup 3 is comprised of five children with other neurodevelopmental disorders and 31 typically developing control children. Subgroup 4 is comprised of three children with suspected FASD and four children with other neurodevelopmental disorders.
in a specificity of 55.4% (95% CI: 43.5%-67.2%) and NPV of 100.0% (95% CI: not applicable). When comparing children with suspected FASD and children with other neurodevelopmental disorders with typically developing control children, the 4-class model resulted in a specificity of 83.8% (95% CI: 71.4%-94.7%) and NPV of 88.0% (95% CI: 79.1%-95.9%). Table 18 for classification function of the 4-class model.

In order to further explore how the diagnostic entities were being grouped in the 4-class model, participant assignment was explored for typically developing control children (n=37), children with ADHD only (n=21), ASD only (n=5), suspected FASD only (n=14) and children with comorbid disorders (n=9). As shown in Table 20, the neurodevelopmental profile did not group participants according to their diagnostic labels. When comparing children with suspected FASD only with typically developing control children, children with ADHD only, ASD only and comorbid disorders, the 4-class model resulted in a specificity of 55.4% (95% CI: 43.1%-67.7%) and NPV of 100.0% (95% CI: not applicable; Table 21). See Figure 11 for a depiction of the mean scores on each of the latent variables included in the LPA for the four distinct diagnostic groups (typically developing control children and children with ADHD only, ASD only and suspected FASD only).

5.4 Discussion

As per the 2-class model, the neurodevelopmental profile correctly identified only 56.9% of typically developing control children and children with other neurodevelopmental disorders as not having FASD (specificity). However, when it came to differentiating children with suspected FASD and children with neurodevelopmental disorders from typically developing control children, the neurodevelopmental profile’s specificity increased markedly, with 83.8%
Table 20. Number of children assigned to each subgroup in the 4-class model (sensitivity analysis)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Typically developing control children (n)</th>
<th>Children with ADHD (n)</th>
<th>Children with ASD (n)</th>
<th>Children with suspected FASD (n)</th>
<th>Children with comorbid disorders (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1</td>
<td>6</td>
<td>10</td>
<td>3</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Subgroup 2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Subgroup 3</td>
<td>31</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subgroup 4</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>21</td>
<td>5</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; FASD: Fetal Alcohol Spectrum Disorder; NPV: negative predictive value; PPV: positive predictive value of typically developing control children being correctly identified as not having FASD or other neurodevelopmental disorders (specificity). Although the specificity increased, it was a trade-off for the neurodevelopmental profile’s NPV, which decreased from 97.4% to 81.6%. With respect to the 4-class model, when compared to the 2-class model, the change in specificity and NPV was insignificant. Further, the 4-class model did not produce subgroups that were reflective of the diagnostic constructs represented in the sample.

Thus, based on the findings of the current study, the neurodevelopmental profile identified by Lange and colleagues (Lange et al., Submitted) was not able to differentiate children with
Table 21. Classification function of the 4-class model (sensitivity analysis)

<table>
<thead>
<tr>
<th>Classification function (%)</th>
<th>FASD vs. Typically developing controls children, children with ADHD, ASD and comorbid disorders&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100.0</td>
</tr>
<tr>
<td>Specificity</td>
<td>55.4 (95% CI: 43.1-67.7)</td>
</tr>
<tr>
<td>PPV</td>
<td>32.6 (95% CI: 19.0-47.5)</td>
</tr>
<tr>
<td>NPV</td>
<td>100.0</td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; FASD: Fetal Alcohol Spectrum Disorder; NPV: negative predictive value; PPV: positive predictive value

<sup>a</sup>Assuming subgroup 1, 2 and 4 are reflective of the neurodevelopmental profile of FASD and subgroup 3 is reflective of typically developing control children and children with other neurodevelopmental disorders suspected FASD from children with other neurodevelopmental disorders, but rather differentiated the clinical participants – i.e., children with suspected FASD, ADHD and/or ASD – from the non-clinical participants – i.e., typically developing control children. When looking at the mean scores on each of the latent variables included in the LPA for children with ADHD only, ASD only and suspected FASD only, rule breaking behavior appeared high in all three groups with very little variation, while the mean scores for the NEPSY-II word generation (letter) and WASI-II similarities and vocabulary subtests were similar for children with suspected FASD only and children with ASD only. These findings suggest that these subtests may not be particularly useful in differentiating children with suspected FASD from children with other neurodevelopmental disorders.
Figure 11. Mean scores on each of the latent variables included in the LPA for typically developing control children and children with ADHD only, ASD only and suspected FASD only

Note. All scores are presented as z-scores.
There are a few limitations of the current study that must be acknowledged. First, the sample size in the current study was small and thus, the inability to differentiate children with suspected FASD from children with other neurodevelopmental disorders may be due to a lack of statistical power. Second, the neurodevelopmental test battery from which the neurodevelopmental profile was derived was predetermined for the purposes of the WHO International Study on the Prevalence of FASD and was not developed for the purpose of identifying a neurodevelopmental profile. Therefore, it is possible that other neurodevelopmental domains are needed or would be better for differentiating these diagnostic groups than the domains modelled in the current study. Third, apart from FASD, the neurodevelopmental diagnoses were ascertained by word of mouth and the criteria used for diagnosis were largely unknown. Moreover, the stepwise process of the WHO International Study on the Prevalence of FASD was optimized to ascertain cases of suspected FASD and as such, children with other neurodevelopmental disorders had a lower probability of being identified and undergoing a full neurodevelopmental assessment – specifically if they were undiagnosed. The implication of this is that the group of children with other neurodevelopmental disorders may not fully be representative of children with ADHD and/or ASD as a whole. Fourth, the groups were not matched on demographic variables like age, gender and ethnicity, which could be related to classification accuracy, and it was not possible to control for potential confounding. Nonetheless, the most notable strength of the current study is the fact the clinical comparison group (i.e., children with other neurodevelopmental disorders) resembled a real-life clinical population more closely than the clinical populations used in previous studies (Mattson et al., 2013; Nash et al., 2011; Nash et al., 2006). For instance, the comparison group of children with other neurodevelopmental disorders used in the current study included children with comorbid diagnoses and was not limited to a single disorder (e.g., ADHD only).
In summary, the current study found that the neurodevelopmental profile identified by Lange and colleagues (Lange et al., Submitted) is not specific to children with FASD and as such, it was not possible to differentiate the diagnostic groups (i.e., children with suspected FASD, ADHD and ASD) from one another based on the identified neurodevelopmental profile and the domains included. The findings are strengthened by the fact that impairments in the domains measured by the subtests included in the neurodevelopmental profile were used in the ascertainment of suspected FASD cases and thus, by default, the group of children with suspected FASD would be more homogenous and less similar to children with other neurodevelopmental disorders. Ultimately, the findings question the uniqueness of FASD with respect to the neurodevelopmental impairments associated with it.
Chapter 6 Discussion
The misdiagnosis of FASD, and in general, has a number of notable consequences. First, it has implications for the pharmacologic and therapeutic approach to treatment. Although no specific treatments exist that are unique for FASD, there are studies comparing children with FASD to children with ADHD with respect to treatment effectiveness, albeit only a limited number (there are no existing studies comparing children with FASD to children with any neurodevelopmental disorders other than ADHD with respect to treatment effectiveness). These studies suggest that children with FASD respond differently to stimulant medication than children with idiopathic ADHD (Doig, McLennan, & Gibbard, 2008; Frankel, Paley, Marquardt, & O’Connor, 2006; O’Malley, Koplin, & Dohner, 2000). Second, misdiagnosis can result in the mismanagement of behavioral symptoms, which could lead to worsening behavior. Third, from an epidemiological point of view, misdiagnosis will result in inaccurate incidence and prevalence estimates, which are necessary to set priorities for public health policy, funding for public health initiatives and health-care planning. Lastly, misdiagnosis can lead to reduced power to detect a clinically meaningful difference between groups in research studies (Astley & Clarren, 2000; Chasnoff et al., 2015).

Supporting the increased likelihood of misdiagnosis among individuals with FASD are the findings from the current thesis project that approximately 53% of children with FASD have co-occurring ADHD, 13% have co-occurring ODD, 7% have co-occurring CD and 3% have co-occurring ASD (Chapter 3). These findings highlight that teratological history should be sought for all children with any neurodevelopmental disorder, especially an externalizing disorder, in order to enhance the differential diagnostic process and provide an accurate and appropriate diagnosis. Further, health care providers should routinely consider prenatal alcohol exposure when assessing and diagnosing behavioral problems – particularly externalizing behavioral 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. For example, certain protective factors such as early diagnosis and intervention, and providing an appropriate environment have been shown to improve outcomes and decrease the risk for adverse outcomes up to fourfold (Paintner, Williams, & Burd, 2012). Commonly observed adverse outcomes – also known as secondary disabilities – among individuals with FASD include mental illness, disrupted school experience (suspension, expulsion, and/or dropout), poor academic achievement and school failure, involvement with the law (trouble with authorities, being charged with or convicted of a crime), confinement (inpatient treatment for mental health and/or substance use problems, or incarceration for crime), alcohol and other drug problems, sexually deviant behavior, problems with employment (either obtaining or maintaining employment) and dependent living (e.g., assisted living or requiring a supervised living environment) (Streissguth et al., 2004). However, it should be acknowledged that diagnosis, whether early or not, is only useful if the necessary interventions are made available to the affected individual.

It is important to recognize that externalizing behaviors 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 behaviors can often be modified by behavior management, whereas impairments are most appropriately managed by accommodations (Paintner et al., 2012). Additional research in this area is needed. However, the co-occurrence of the examined neurodevelopmental disorders (ADHD, ASD, CD and ODD) and FASD likely represent many complex cases, which deserve timely and tailored intervention. The presence of these co-occurring disorders creates significant challenges for health care professionals in terms
of screening, assessment, differential diagnosis and treatment. It must also be acknowledged that children with FASD often receive multiple diagnoses before they are appropriately assessed and diagnosed with FASD (Chasnoff et al., 2015).

It has been argued that a large portion of existing FASD cases is undiagnosed, even in clinical settings where FASD is an important area of emphasis (Chasnoff et al., 2015). As discussed above, this is likely due to the difficulty of diagnosing FASD, as there is no standardized set of diagnostic criteria, a high rate of comorbidity (Lange et al., 2018; Popova et al., 2016), and individuals with FASD exhibit signs and symptoms that overlap those of other neurodevelopmental disorders (McLennan, 2015). This is further complicated by the fact that obtaining accurate prenatal alcohol exposure history is not an easy task. For instance, recalling the amount of alcohol consumed and the frequency at which it was consumed during a past pregnancy, especially when questioned years later, can often be inaccurate and incomplete (recall bias). Further, alcohol use during pregnancy is a highly stigmatized behavior and is often underreported. It is the diagnostic difficulty of FASD that has ultimately led to the pursuit of identifying a unique neurodevelopmental profile, as the ultimate aim is to improve our ability to accurately diagnose it.

The identification of a unique neurodevelopmental profile of FASD would aid in the accurate identification of individuals with FASD, by adding to the armamentarium of clinicians. The accurate identification is not only beneficial to the affected individual in terms of facilitating appropriate treatments and interventions, it can also help prevent subsequent FASD-affected births by providing appropriate interventions, treatment, counseling and support for birth mothers of children diagnosed with FASD (Astley et al., 2000). Appropriate screening strategies may also facilitate early recognition and intervention for other affected siblings (Astley et al., 2000).
Further, the identification of a distinct neurodevelopmental profile, which is pathognomonic of FASD, would have a number of notable clinical implications. First, a unique neurodevelopmental profile would aid in the differential diagnosis process by facilitating the discrimination of FASD from other neurodevelopmental disorders. Second, a unique neurodevelopmental profile would ultimately lead to the ascertainment of accurate FASD prevalence estimates. Third, a unique neurodevelopmental profile would assist in the development of appropriate targeted interventions for children with FASD. Lastly, identifying a unique neurodevelopmental profile of FASD would result in the enhancement of clinical services to this population. Coupled with the fact that the neurodevelopmental assessment is both time consuming and costly (Popova et al., 2013), the current capacity of diagnostic services is also limited (Clarren, Lutke, & Sherbuck, 2011), or even completely absent in some countries. Thus, delineating a unique neurodevelopmental profile of FASD would have the ability to assist in triaging children who would be most in need of a full clinical assessment (i.e., an individual positively screened for FASD will ideally then undergo a full diagnostic evaluation for FASD), and could even reduce the time it takes to fully assess an individual (Nash et al., 2011; Nash et al., 2006).

The finding from the current thesis project that a neurodevelopmental profile exists that can differentiate children with suspected FASD from typically developing control children with a high degree of classification accuracy (see Chapter 4) is in line with previous studies which demonstrated that the neurodevelopmental effects of prenatal alcohol exposure can be used to distinguish alcohol-affected children (both dysmorphic and non-dysmorphic) from typically developing children (Mattson et al., 2010, 2013; Nash et al., 2006, 2011). As the current thesis project is the first to analyze both behavioral observations/ratings and performance-based measures of neurodevelopment when attempting to identify a
neurodevelopmental profile of FASD, comparing the findings to previous studies is difficult. However, as discussed in great detail above (see Chapter 1), the two approaches that have previously been taken to determine whether a unique neurodevelopmental profile of FASD exists involve the utilization of either behavioral observations/ratings by parents/caregivers or subtest scores from standardized test batteries assessing a variety of neurodevelopmental domains. Both approaches have shown some promise, with the former approach having good sensitivity (63% to 98%), but varying specificity (42% to 100%), and the latter approach having good specificity (72% to 96%), but varying sensitivity (60% to 88%). As found in the current thesis project, using a combination of behavioral observations/ratings and performance-based measures of neurodevelopment did yield both a sensitivity and specificity that were significant (95% and 89%, respectively).

Further, even though the mean IQ for children with suspected FASD was found to be significantly different from the mean IQ of the typically developing control children in the current project, the neurodevelopmental profile was more accurate at group classification than IQ scores alone. This finding is also in line with the findings of Mattson and colleagues (Mattson et al., 2010), who performed a hierarchical logistic regression to determine whether their neurodevelopmental profile improved prediction of group membership above and beyond IQ. In their analysis, IQ was significantly associated with group membership, (OR = 0.90, 95% CI = 0.87-0.94), and accounted for an overall diagnostic accuracy rate of 76%. However, a significant improvement in classification accuracy was evident when the other neurodevelopmental measures were included in the model – classification accuracy increased to 92%.

Unfortunately, the current thesis project subsequently found that the neurodevelopmental profile was not able to differentiate children with suspected FASD from children with other
neurodevelopmental disorders (i.e., children with ADHD and/or ASD; see Chapter 5).

Rather, the neurodevelopmental profile more accurately classified children with neurodevelopmental disorders (i.e., children with suspected FASD, ADHD and/or ASD) from children without neurodevelopmental disorders (i.e., typically developing control children). Thus, the FASD-sensitive neurodevelopmental profile was not specific to children with FASD, suggesting that a neurodevelopmental profile that can differentiate children with FASD from children with other neurodevelopmental disorders may not exist. Despite the relatively small sample size, the latent profile analyses produced statistically and clinically significant results.

That being said, the 4-class model did result in children with neurodevelopmental disorders being broken down into subgroups. However, they were not grouped according to their diagnostic categories. The subgrouping that occurred could have simply been an artifact of the methodology used, as the primary goal of LPA is to maximize the homogeneity within subgroups and the heterogeneity between them. Accordingly, the 4-class model would have been “forced” to identify four response patterns associated with the observed continuous variables in the dataset, regardless of whether or not the said patterns were clinically meaningful.

Even though variable selection was based on a method of high reliability and transparency, the findings are limited by the measures available for analysis and the resulting profile could exclude additional measures that may be particularly useful for differentiating children with FASD from children with other neurodevelopmental disorders. As mentioned, the data utilized were from a neurodevelopmental test battery that was developed for the purpose of screening children for FASD among a population-based sample and was restricted in scope (i.e., it was developed for the WHO International Study on the Prevalence of FASD to
screen for children with suspected FASD and not as a comprehensive diagnostic test battery). Thus, the findings are limited by the measures used in the analyses, as the inclusion of additional measures may have resulted in a more specific FASD neurodevelopmental profile. Also, it would have been advantageous if the neurodevelopmental profile’s specificity could have been tested on a new sample (i.e., a different sample than that on which it was identified); however, this was simply not possible.

While it is well-established that prenatal alcohol exposure is the cause of FASD, not all infants exposed to alcohol prenatally are born with the disorder. For instance, it was recently estimated that one in 13 infants exposed to alcohol prenatally will be born with FASD (Lange, Probst, Gmel, et al., 2017); suggesting that there are other factors involved with respect to fetal susceptibility such as, genetics (Eberhart & Parnell, 2016). Compelling evidence of the role genetics plays in the susceptibility of FASD development was the work of Streissguth and Dehaene (Streissguth & Dehaene, 1993) in the early nineties. In their study of monozygotic and dizygotic twins of alcoholic mothers, monozygotic twins were 100% concordant for a FAS diagnosis while dizygotic twins were only 64% concordant, despite equivalent alcohol exposure within twin pairs. Thus, these data were interpreted as reflecting the modulating influence of genes in the expression of the teratogenic effects of alcohol. With respect to the genetics underlying FASD susceptibility, studies have shown that in humans Alcohol Dehydrogenase (ADH) alleles predicted to metabolize ethanol more quickly protect against FASD. For example, Viljoen and colleagues (Viljoen et al., 2001) found that the ADH1B*2 allele was significantly more common in the mothers of the control group than in the mothers of the FAS-affected children. Further, maternal genotypes with at least one ADH1B*3 allele have been found to be correlated with a lower incidence of FASD (Das, Cronk, Martier, Simpson, & McCarver, 2004; Jacobson et al., 2006). Thus, there is
evidence to support the idea that fetal susceptibility is at least partially dependent on the mother’s genetics regarding alcohol metabolism.

It is also evident that prenatal alcohol exposure leads to epigenetic changes (i.e., altered gene expression) and it is hypothesized that these changes may contribute to the spectrum of effects and different phenotypes observed in children with FASD (Liyanage, Curtis, Zachariah, Chudley, & Rastegar, 2017). Genetic factors and epigenetic mechanisms such as DNA methylation, histone post-translational modifications and noncoding RNAs have been shown to contribute to the gene expression changes caused by prenatal alcohol exposure in both humans and animal models (Liyanage et al., 2017). Although this area of research is still in its infancy, it is clear that the discovery of reliable genetic and epigenetic markers for FASD would have significant implications for its diagnosis. Further, such discoveries could aid in the development of specific therapeutic interventions, as currently, research-based interventions for this population are lacking (Paley & O’Connor, 2011).

This line of investigation should not be restricted to FASD, but rather should be applied to all neurodevelopmental disorders, as a paradigm shift has occurred in that neurodevelopmental disorders are no longer viewed as having a psychogenic etiology but rather a genetic etiology. For example, Glessner and colleagues (Glessner et al., 2017) recently examined copy number variants in five neurodevelopmental and neuropsychiatric cohorts, which included schizophrenia, bipolar disease, ADHD, ASD and depression. Duplications of DOCK8 and KANK1 genes were found to be elevated in all five cohorts, implicating that these genes may play a role in neurodevelopment and thus, suggesting a common etiology for these five clinically distinct conditions.

Advances in the understanding of genetics and its role in neurodevelopmental disorder risk are providing a more advanced framework for deciphering etiologies. Although it is known that prenatal alcohol exposure is the cause of FASD, the genetic etiology of FASD remains
unknown. It is possible that in the future reliable genetic markers will be identified for all neurodevelopmental disorders, including FASD. However, at this time, investigating the existence of a distinct neurodevelopmental profile of FASD is still worthy of attention.
Chapter 7 Conclusion and Future Directions
The results of this thesis project indicate that while children with suspected FASD could be differentiated from typically developing children with a high degree of accuracy, it was not possible to differentiate children with suspected FASD from children with other neurodevelopmental disorders using the neurodevelopmental measures utilized in the current neurodevelopmental profile. Although the neurodevelopmental profile’s classification function was better when differentiating children with neurodevelopmental disorders (i.e., children with suspected FASD, ADHD and/or ASD) from typically developing control children, these neurodevelopmental conditions do not appear to be synonymous. However, it should be acknowledged that the sample size in the current project was small and given that small sample sizes can lead to erroneous conclusions, the current neurodevelopmental profile should be tested on a larger sample.

The differentiation of children with FASD from children with other neurodevelopmental disorders is important for the provision of an accurate diagnosis and determination of the most appropriate pharmacologic and therapeutic approach to treatment. Given that the FASD-sensitive neurodevelopmental profile identified in the current project was not specific to children with suspected FASD, additional research is needed to determine whether a neurodevelopmental profile exists that is unique to FASD and able to distinguish children with FASD from children with other idiopathic neurodevelopmental disorders. Future studies should investigate whether a different set of neurodevelopmental and behavioral measures altogether or whether the combination of the current profile and other measures would be able to successfully differentiate children with FASD from children with other neurodevelopmental disorders. Such studies should cover a broader array of neurodevelopmental and behavioral domains than those assessed in the test battery utilized in the current project.
If future studies identify a unique neurodevelopmental profile of FASD, there are a few areas of study that will have to be addressed prior to its clinical implementation. First, potential gender and age differences will need to be explored. Second, the cross-cultural utility of the profile will need to be established. Third, the possibility that individuals with FASD exhibit more than one neurodevelopmental profile will also need to be explored – for instance, each of the diagnoses within the spectrum could have their own profile. Such studies would need a much larger sample size, and could only be achieved by way of a big data strategy, where very large groups of individuals are brought together and identified using a common diagnostic system (or at least with data available so they are classifiable according to several different, well-defined diagnostic systems) and then neurodevelopmental profiles are examined with statistical adjustment for potential confounders. Lastly, there are a number of other factors that need to be taken into consideration before a neurodevelopmental profile unique to FASD can be truly identified and validated, namely: genetic factors/differences in fetal susceptibility to prenatal alcohol exposure, information on dosage and timing of exposure, other adverse prenatal exposures (e.g., prenatal tobacco and/or drug exposure), postnatal experiences (e.g., abuse and neglect), neurodevelopmental inheritance (i.e., the possibility that some neurodevelopmental impairments are inherited from the parents) and maternal and paternal psychopathologies.

Given the possibility that a neurodevelopmental profile unique to FASD may not exist, it should be explored whether neurodevelopmental data combined with other types of data such as, genetic, epigenetic and/or brain imaging data would produce a profile that is able to diagnose and differentiate FASD from other neurodevelopmental disorders, and to aid in the development of specific therapeutic interventions. This approach is in line with the Research Domain Criteria (RDoC) initiative launched in 2009 by the National Institute of Mental Health (Insel et al., 2010). The RDoC is a framework for research that is intended to promote the
investigation and characterization of mental disorders through a better understanding of their neurobiological mechanisms. Given the recent paradigm shift with respect to how neurodevelopmental disorders are viewed – i.e., neurodevelopmental disorders are being viewed as having a genetic etiology rather than a psychogenic etiology – researchers are now focusing on advancing our understanding of genetics and its role in neurodevelopmental disorder risk (Glessner et al., 2017). FASD is not an exception to this point of view. Although it is well known that prenatal alcohol exposure is a necessary cause of FASD, the genetic etiology of FASD remains unknown. The discovery of reliable genetic and epigenetic markers for FASD would have significant implications for its diagnosis. Given the attributes of RDoC, it is ultimately intended to inform the development of future classification schemes for mental disorders. As such, it is possible that in the future the current diagnostic categories will be redefined according to their biology – that is to say, the current categorical entities used to classify mental disorders, including neurodevelopmental disorders may be refined to be more reflective of biologically homogeneous groups (Insel et al., 2010).
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