

Prenatal Alcohol and Nicotine Exposure and the Subsequent Cognitive and Behavioral  
Deficits Seen in Children

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### Abstract

Prenatal alcohol and nicotine exposure have well known physiological effects on the fetus. However, it is the goal of this thesis to inform the reader of the deleterious effects that these substances can have on cognitive and behavioral development in children. A literature review in relation to this topic was conducted through online databases using key words. Though some of the results were inconsistent, enough evidence exists for women to be educated on the increased risks for cognitive and behavioral deficits in children exposed to alcohol and nicotine in utero.

## Prenatal Alcohol and Nicotine Exposure and the Subsequent Cognitive and Behavioral Deficits Seen in Children

Alcohol and tobacco smoke are known to have deleterious effects on birth outcomes in neonates born to women who have used these substances during pregnancy. However, research is indicating that the effects of these legal substances are manifold and persist throughout childhood, possibly even into adulthood. The aim of this thesis is to show that prenatal alcohol and nicotine exposure cause cognitive and behavioral deficits that can be seen throughout childhood. The following pages will describe the researched biological effects of alcohol and nicotine on the developing fetus. This will be followed by a literature review of studies researching the effects of prenatal alcohol and nicotine exposure on cognition and behavior in children.

### **Biological Effects of Alcohol**

Alcohol exposure causes damage to the central nervous system (CNS) of the developing fetus. Depending on the timing and amount of exposure, there may be different effects. This results in the variation in symptoms that are present in fetal alcohol spectrum disorders (FASD). New magnetic resonance imaging (MRI) technologies are being used to track brain changes in people exposed to alcohol prenatally, which has enabled discoveries related to specific areas of the brain and how they respond to alcohol exposure (Warren, Hewitt, & Thomas, 2011). Up to this point, a few of the regions that have been noted to be especially vulnerable include the frontal cortex, regions of the cerebellum, the corpus callosum, and the hippocampus. A certain type of MRI, known as diffusion tensor imaging (dtMRI), is able to notice changes in white matter nerve tracts. These changes in children with prenatal alcohol exposure

(PAE) are thought to be related to alterations in information processing (Warren et al., 2011).

As stated in Warren et al. (2011), embryonic frog models exposed to alcohol experienced altered gene expression leading to microcephaly, growth retardation, and microphthalmia. In humans, the oxidative stress that is induced by prenatal alcohol exposure may cause altered timing of apoptosis which can interfere with neuronal development, possibly leading to the above symptoms.

Abnormalities have been found in the size of the corpus callosum as a result of alcohol exposure, leading to difficulties in verbal learning in this population. In addition, alcohol may cause basal ganglia volume reduction. This effect may result in lower intelligence quotient (IQ) scores. Other research suggests teratogenic effects of alcohol on the cerebellum, resulting in fine and gross motor delays and therefore affecting balance and motor control in this population (Coles, 2011; Dorrie, Focker, Freunsch, & Hebebrand, 2014).

### **Biological Effects of Nicotine**

Nicotine is one of the many compounds present in tobacco smoke. It has the ability to cross both the placental and the blood-brain barriers in the developing fetus and it has been found at a 15% higher concentration in the fetus than in the mother. When the developing fetus's central nervous system (CNS) is exposed to nicotine, the nicotinic acetylcholine receptors (nAChR) are stimulated, triggering neurodevelopmental events. Therefore, the normal timing of these neurodevelopmental processes, such as the migration of nerve cells and the initiation of axons and dendrites, is altered because

nicotine produces the actions that are usually initiated by acetylcholine. As a result, abnormal changes are made within the CNS (Blood-Siegfried & Rende, 2010).

Nicotine also desensitizes neurotransmitter action in prenatal exposure and decreases epinephrine and norepinephrine production. Due to neurotransmitter reduction in areas such as the frontal cortex, the fetus may be predisposed to conditions like attention deficit/hyperactivity disorder (ADHD). In ADHD, children have the inability to suppress input, which is related to dysregulation of neurotransmitters in the frontal cortex and, therefore, the inability to regulate impulse control and stimuli. Because of nicotine's effects on neurotransmitters, ADHD in children who were prenatally exposed to tobacco smoke may be directly related to nicotine (Blood-Siegfried & Rende, 2010).

In addition, alterations in the serotonergic and dopaminergic pathways can lead to emotional dysregulation, leading to the externalizing behaviors seen in many children who were prenatally exposed to nicotine. These behavioral traits may also be linked to a greater risk for mental illness in this population, including an increased prevalence of nicotine addiction. Learning deficits are also found in children prenatally exposed to nicotine. The hippocampus, the part of the brain involved in sequential learning and short-term memory, is thought to be damaged by prenatal nicotine exposure, therefore leading to these deficits. However, the hippocampus continues to develop after birth. Because of this, it is hypothesized that postnatal smoking may also contribute to cognitive deficits (Blood-Siegfried & Rende, 2010; Ellis, Berg-Nielsen, Lydersen, & Wichstrom, 2012).

### **Prenatal Alcohol Exposure and the Literature**

The following information was collected from research articles published within the last five years. A search was conducted through CINAHL Plus using key words in order to obtain peer-reviewed journal articles. Specific information on these articles can be found in Table 1 in the appendix.

#### **Purpose and Patient Population**

Studies on the cognitive and behavioral effects of PAE have been conducted all over the world. Robinson et al. (2010) studied 2,868 pregnant women and their children at an obstetric hospital in Western Australia. However, only 1,860 mother-child pairs were able to participate all the way through the study. The children in this study were born between 1989 and 1991 and a 14-year follow up study evaluated them between 2003-2006, as well as at the ages of two, five, eight, and ten. This longitudinal study assessed the relationship between prenatal alcohol exposure and child behavioral development, with a specific focus on light-moderate drinking.

Another longitudinal study in this review studied 2,264 mother-child pairs from a Swedish antenatal clinic. Again, only 1,868 women participated at the second follow up, which was at 32 weeks' gestation. Though this is a longitudinal study as well, it is only in the beginning stages, therefore the current information only details intra-pregnancy alcohol consumption, the labor process, and characteristics of the newborns. This is an ongoing study that is being used to determine the effects of low-moderate maternal alcohol intake on the neuropsychological development of the child over time (Comasco, Hallberg, Helander, Orelund, Sundelin-Wahlsten, 2012).

Proven, Ens, & Beaudin (2014) analyzed the language abilities, including strengths and weaknesses, of 124 school-aged children with a clinical diagnosis of Partial Fetal Alcohol Syndrome (pFAS) or Alcohol Related Neurodevelopmental Disorder (ARND). These children resided in Canada and their ages ranged from five to eighteen. Within this study, a specific focus was placed on age and gender and the specific effects of prenatal alcohol exposure in these populations. Graham et al. (2013) studied the presence of sluggish cognitive tempo (SCT) in children with PAE and with or without ADHD. Two hundred and seventy-two children between the ages of eight and sixteen, along with their caregivers, were recruited from five different sites across the United States in order to determine if an association exists between PAE and decreased cognitive abilities.

The focus of a study by Peles et al. (2014) was to determine the effects of and compliance to a Brief Intervention, which involved the interviewer explaining to the women the harmful effects of alcohol and other substance abuse upon both them and their babies and giving them tips for cutting down and quitting. These 108 Israeli women were recruited at less than or equal to 30 weeks' gestation as a result of presenting to a hospital in Israel with medical complications. Though Peles et al. did not conduct a longitudinal study, their research did provide insight on the confounding factors in the family environment that may contribute to the development of behavioral disorders in children exposed to alcohol prenatally.

A similar study was conducted as a cohort study of 907 mother-child pairs in Dublin, Ireland from 2010-2011. The intent was to determine if women heed the medical advice of their midwives to abstain from alcohol while pregnant and breastfeeding.



Again, this study contributed information regarding the correlations between specific maternal characteristics and alcohol consumption during pregnancy (Dunney, Muldoon, & Murphy, 2015).

The other research articles in this review provided more focused information from different studies on the neurobehavioral profile of children who have been exposed to alcohol prenatally. Jacobson, Carter, & Jacobson (2013) gave a commentary on the behavioral effects of prenatal alcohol exposure observed by Day and colleagues throughout childhood and into young adulthood. Pei, Denys, Hughes, & Rasmussen (2011) surveyed the prevalence of mental health issues seen in people with fetal alcohol spectrum disorders (FASD). The classification of FASD encompasses multiple disorders, but there is not a profile that is specific to behavioral deficits. Mattson & Riley (2011) conducted a review in order to obtain more information on establishing a neurobehavioral profile of affected individuals who do not show physical signs of prenatal alcohol exposure. Their goal was to develop criteria that would aid in the identification and prompt treatment of these children.

Coles (2011) discussed the barriers to detecting FASD in children and sought to provide ways to distinguish between behavioral and developmental disorders caused by prenatal alcohol exposure vs. other causes. Another review, by Dorrie et al. (2014), focused on the central nervous system consequences of PAE. In addition, new research advances are being made regarding the long term effects of PAE and Warren et al. (2011) highlight these advances.

## Methods

The majority of these studies gathered information through parental questionnaires and interviews with the parent(s), although sometimes the child was involved in the process as well. Assessment of prenatal alcohol exposure was primarily conducted through the use of a self-reporting tool called the Alcohol Use Disorders Identification Test (AUDIT). Comasco et al. (2012), Dunney et al. (2015), and Peles et al. (2014) specifically cited the use of this tool. This questionnaire consists of ten items that assess the quantity and frequency of maternal alcohol exposure during pregnancy. Due to the information often being gathered after pregnancy, the data collected from the AUDIT is retrospective data, which carries with it a level of bias. Despite the possibility of false reporting, the AUDIT is a well established tool that has been useful in obtaining results regarding PAE.

There are two main ways of determining prenatal alcohol exposure. The first is through maternal report, either prospectively or retrospectively, as mentioned above. The second is through a dysmorphology examination, which involves documenting physical markers such as short palpebral fissures, a smooth philtrum, a thin vermilion border, and small brain size. These characteristics are thought to be associated with heavy alcohol exposure during a specific time frame in the first trimester, resulting in the profile that is known as Fetal Alcohol Syndrome (FAS). However, as this thesis argues, there are behavioral and cognitive deficits that result from PAE, even in those children who do not have these physical characteristics. Therefore, it is necessary to determine a more accurate tool for assessing PAE in order for the disorder to be acknowledged in children whose mothers may give a false report (Mattson & Riley, 2011).

A few studies used the identification of alcohol metabolites in neonatal meconium samples to determine PAE. In Jacobson et al.'s (2013) commentary on Day and colleagues longitudinal study, they noted that maternal self-report of alcohol consumption was validated by recognized cognitive defects in the children, as well as alcohol metabolites in meconium samples. This validation is ideal; however, Mattson & Riley (2011) stated that testing for metabolites in meconium is only helpful for determining the presence of alcohol exposure later in pregnancy.

The Child Behavior Checklist (CBCL) was used by Robinson et al. (2010) and Graham et al. (2013) to evaluate emotional and behavioral problems in children at different ages. This questionnaire is usually filled out by the parent(s) of the child, but in some cases the researchers also had the child's school teacher fill it out. The results were similar enough, though, that the conclusions were drawn from the parental questionnaires. When completed, the CBCL provides three z-scores, each of which corresponds with either total behavior, internalizing behavior, or externalizing behavior. The higher the score, the more problematic the child's emotions and behaviors (Robinson et al., 2010).

In addition to the CBCL, Graham et al. (2013) used the Sluggish Cognitive Tempo (SCT) questionnaire to assess cognitive ability. The SCT tool is used to reveal deficits in sustained attention, including sluggishness, hypoactivity, varying alertness, and daydreaming. High SCT scores are associated with internalizing behaviors, such as depression, anxiety, obsessions, and social phobias. This questionnaire is filled out by the parents.

In the study by Proven et al. (2014), the Clinical Evaluation of Language Fundamentals (CELF-4) was used to assess the language profile of school-aged children exposed to alcohol prenatally. Different test forms were used for different age groups. Score categories for the CELF-4 include the Core Language Score, which quantifies the child's general language ability, and the language indices, which include five subcategories (receptive language, expressive language, language content, language structure, and language memory) that give more detailed information on language and communication. Language delay is rated as severe, moderate, mild, average, or above average.

### **Discussion**

In the research on PAE and the associated behavioral and cognitive effects in children, it is difficult to establish strictly causative relationships between these deficits and PAE. However, many correlations and associations are present and conclusions may still be drawn from this data.

Multiple studies in this review found a positive correlation between nicotine use and drinking during pregnancy, including Comasco et al. (2012). This finding was supported by Dorrie et al. (2014), with the additional associations of multiple substance use, low socioeconomic status, greater mean age, fewer prenatal visits, and a greater total amount of years of alcohol consumption. Similar to the association with low socioeconomic status, Petes et al. (2014) found that women who drank during pregnancy were less educated and less likely to be in a relationship. In Dunney et al. (2015), older age (35-39), smoking, private health care, and a history of illicit drug use were also positively correlated with alcohol consumption. Robinson et al. (2010) found specifically

that a higher alcohol intake during the first trimester was associated with smoking during pregnancy. The above findings indicate the possibility of other factors playing a role in the development of neurobehavioral disorders in children subject to PAE.

The longitudinal study of behavioral development by Robinson et al. (2010) revealed interesting findings regarding the effects of low to moderate PAE. Both light and moderate drinking at 18 weeks gestation resulted in a decrease in CBCL scores, indicating better behavior. In addition, fewer behavioral problems were noted over 14 years in children whose mothers were light drinkers (two to six standard drinks per week) during their first trimester than in children whose mothers did not drink at all. The authors suppose that the self-control that is necessary to engage in light-moderate drinking may be a factor that speaks to the parenting skills of the mother, therefore resulting in better behavior in these children. As many pregnancies are unexpected, this study may be able to give peace of mind to those mothers who continue drinking during their first trimester because the pregnancy is unexpected and they did not know that they were pregnant.

However, Robinson et al. (2010) and others also found supporting evidence for the detrimental effects of PAE on behavior. Both occasional drinking at 34 weeks gestation and heavy drinking at any time resulted in higher CBCL scores in children, indicating poorer behavior. With heavy drinking, increased behavioral problems were noted in children in all three categories (total, internalizing, and externalizing), but these results were not statistically significant due to the small sample size of heavy drinkers studied. According to Matson & Riley (2011), compared to other children with similar traits (such as low intelligence quotient [IQ]), alcohol-exposed children experienced

impairment in externalizing behaviors and adaptive skills. Due to these findings, conduct disorder is common in this population. However, Dorrie et al. (2014) propose that the risk for this disorder can be reduced if the children are raised in stable homes.

Language is another area that was highly reported about by these studies. Proven et al. (2014) discovered that almost 70% of the children they studied with pFAS or ARND scored a rating of “severe” on the Core Language Index, indicating communication impairments. In addition, there were no significant differences in language scores among the two diagnoses (pFAS and ARND). These children showed poor performance in both expressive and receptive language abilities. Dorrie et al. (2014) also noted that reduced language comprehension and some hearing impairments have been discovered in this population, which would contribute to a delay in language development.

Coles (2011) defined issues that PAE can cause in a child’s memorization capabilities. These children tend to have problems with learning new material and with memorization, due to deficits in executive functioning, such as in active working memory, planning, problem solving, and organization. Though they have normal long-term memory abilities, achieving this level of memory may take more trials because these children process information more slowly and therefore require more time to attain mastery. Visual-spatial deficits have also been noted in this population, often indicated by problems with handwriting, clumsiness, and mathematics. Dorrie et al. (2014) supported this finding by stating that mathematics is often a problem area for children with FASD, due to the inability to mentally represent and manipulate numbers.

Some of these studies also attempted to determine the differences in ADHD in children exposed to alcohol prenatally as compared to other children with ADHD.

Mattson & Riley (2011) discovered that alcohol exposed children had greater impairments related to visual-spatial reasoning, problem solving, and flexibility, as well as encoding and shift aspects of attention. Coles (2011) described difficulties in children with FASD in regulating arousal and in self-control, which often manifests as ADHD. However, with FASD alone, children have fewer behavioral problems but greater deficits in the encoding of information and in being able to effectively switch tasks. In ADHD, the problems lie in focus and sustaining attention. Dorrie et al. (2014) conveyed these same findings in relation to the differences between the neurobehavioral profiles of children with FASD and children with ADHD. Graham et al. (2013) reported that some of the items on the SCT tool were higher (indicating greater cognitive deficits) in children exposed to alcohol prenatally, independent of ADHD status, indicating the possibility to use this tool to determine characteristics of PAE in children who do not have ADHD.

Jacobson et al. (2013) and Pei et al. (2011) both found that the effects of PAE continue throughout childhood and even into adulthood. Specifically, this population is at high risk for psychiatric diagnoses and these symptoms may be more likely than other symptoms of FASD to persist into adulthood. The development of psychiatric disorders may be due in part to the deficits in emotional executive functioning which can manifest in social interactions and decision making skills, as stated by Dorrie et al. (2014).

Mattson & Riley (2011) came to a similar conclusion, based upon the fact that children exposed to alcohol prenatally displayed impairment in social cognition and facial emotion processing ability.

**Limitations**

Research studies are never all-encompassing. Therefore, limitations that complicate the interpretation of the results are inevitable. One of the greatest limitations among these studies is the possibility for response bias, as alcohol consumption during pregnancy was self-reported. Coles (2011) reported that, in some cases, underdiagnosis of FASD may be related to the unreliability of exposure information that is obtained, due to many children presenting later in life and being removed from their biological mother by that time. Dysmorphic features are sometimes subtle and therefore may also be underreported, as noted by Warren et al. (2011). Computer recognition of these features is being developed in order to aid in underdiagnosis in children with dysmorphic features. Underreporting of alcohol use and/or neurobehavioral symptoms must be accounted for when interpreting the results of these studies.

Another limitation found in most of these studies was the inability to control for confounding factors. There are many environmental and genetic factors, such as the caregiving environment, comorbid diagnoses, parental disorders, etc., that may play a role in the development of neurobehavioral disorders in this population of children. Coles (2011) explains that, at present, there is no way to determine whether comorbidities such as ADHD, depression, etc. are the direct results of PAE or if they are due to a combination of genetics, environment, and exposure. For instance, in the study by Proven et al. (2014), comorbid diagnoses and the child's environment were not even analyzed in the study. There are many factors that contribute to the development of children with FASD and it is unfortunately impossible at present to control for all of these factors.



A few of these studies, including Comasco et al. (2012) and Dunney et al. (2015), experienced a loss of a portion of their participants throughout the study. They determined that their losses were random and not pertaining to a specific population, but it is still an important limitation to note. In addition, many of the sample sizes of children and/or mothers were small, namely Peles et al. (2014), Proven et al. (2014), and Graham et al. (2013).

Although some of the studies were longitudinal, those that were not were forced to rely upon an increased amount of retrospective data. Proven et al. (2014) reported a specific limitation in their data collection tool, the CELF-4, because it has not been used much to date for research analysis purposes. Lastly, Robinson et al. (2010) noted a limitation in their assessment of specific patterns of drinking, such as binge drinking, due to data on weekly drinking being obtained as an average. Therefore, data related to the specific timing and volume of alcohol exposure is unknown.

### **Conclusion**

The results from the above studies have shown many detrimental neurobehavioral effects of PAE in children. Even though some of the results were inconsistent, there is enough evidence, though not related to a proven causative relationship, that children are at a significant risk for developing cognitive and behavioral deficits when exposed to alcohol prenatally. This knowledge should be an encouragement to healthcare professionals to impress upon their patients that there is no safe level of PAE. Women need to be properly educated regarding the harmful effects of alcohol consumption during pregnancy on the neurobehavioral development of their children. In addition, as Dorrie et al. (2014) suggest, physicians and psychiatrists need to consider FASD related

diagnoses more frequently when children present with developmental delays and behavioral disorders. Accurate diagnosis will enable more proper and focused treatment of these children.

### **Prenatal Nicotine Exposure and the Literature**

The following articles were collected in the same manner as the previous set, using different key words. This search was used to determine the results of research regarding the cognitive and behavioral effects throughout childhood of prenatal nicotine exposure via tobacco smoke. Specific information on these articles can be found in Table 2 in the appendix.

### **Purpose and Patient Population**

All of these studies are retrospective in nature, meaning that the children were evaluated based upon maternal report of prenatal nicotine exposure. Motlagh et al. (2010) studied 222 children between the ages of seven and eighteen with either ADHD, Tourette's Syndrome, both conditions, or neither condition. The purpose of this study was to assess the pre- and perinatal risk factors associated with ADHD and Tourette's, with heavy maternal smoking being one of the supposed risk factors.

Mei-Dan et al. (2015) conducted a study in Montreal, Canada, surveying women who gave birth from 2001-2007. Out of these 20,938 deliveries, 1,646 of them were to smoking mothers. The goal was to assess for a dose-response relationship between perinatal outcomes and maternal smoking. Though this study did not follow the babies throughout childhood, the risk for dose-related adverse outcomes was assessed. Ellis et al. (2012) studied four year-old children in Trondheim, Norway to determine if a relationship exists between prenatal smoking and psychiatric disorders in preschoolers.

All children born in 2003 and 2004 in Trondheim were invited to participate. Nine hundred and ninety-five parent-child pairs participated all the way through the study.

Yang, Decker, & Kramer (2013) worked with a cohort of Belarusian children around six and a half years of age who were either exposed prenatally to maternal smoking or exposed postnatally to maternal or paternal smoking. The purpose of this study was to find relationships between prenatal and postnatal tobacco smoke exposure and growth and development in the children. A cohort study by Ruckinger et al. (2010) was similar, except that the children studied were ten years-old and the goal was to specifically determine the behavioral problems in these children and the relationship that these problems had to prenatal and/or postnatal tobacco exposure. These children and their parents were from Munich or Wesel, Germany, and the children were born between 1995 and 1998. Five thousand nine hundred and ninety-one children began the study, but only 2,862 had completed information throughout the whole study.

A Swedish study by Lundberg et al. (2010) analyzed 172,182 conscripted males around 18 years of age that were born to Nordic mothers. The goal was to determine the association between prenatal maternal smoking and young adult intellectual outcomes, taking into account parental and birth characteristics. In order to control for familial factors, 14,722 of these males were sibling pairs. Both Cope (2015) and Tiesler & Heinrich (2014) performed reviews on the relationship between prenatal nicotine exposure and the behaviors and adverse effects that result in the exposed children.

## **Methods**

The most common method used to detect nicotine exposure in these studies was maternal self-report. Motlagh et al. (2010), Mei-Dan et al. (2015), Ellis et al. (2012),

Lundberg et al. (2010), Yang et al. (2013), and Ruckinger et al. (2010) all utilized this retrospective method. In Ruckinger et al. (2010), mothers were classified as heavy smokers if they smoked greater than five cigarettes per day and light smokers if they smoked less than five cigarettes per day. Tiesler & Heinrich (2014) reported that nicotine and/or its metabolites can also be detected in the urine, cord serum, meconium, amniotic fluid, hair, or nails. However, these methods may not be as effective because they can only detect recent exposure.

Three studies, Ellis et al. (2012), Ruckinger et al. (2010), and Yang et al. (2013), utilized the Strengths and Difficulties Questionnaire (SDQ) to assess child behavior. The SDQ consists of five behavioral scales related to emotional symptoms, conduct problems, hyperactivity/inattention, peer-relationship problems, and a prosocial scale. Yang et al. (2013) also used the Weschler Abbreviated Skills of Intelligence (WASI) to determine cognitive ability. In Lundberg et al. (2010), intellectual performance in the cohort of male participants was tested in four dimensions: logical/inductive, verbal, spatial, and theoretical/technical.

In addition to using questionnaires, Ellis et al. (2012) utilized the Preschool Age Psychiatric Assessment and conducted semi-structured diagnostic interviews with the child and parent(s). When interpreting their results, these researchers controlled for parental confounders such as personality disorders, anxiety, depression, alcohol use, incarceration, capacity to pay bills, etc.

## **Discussion**

Ruckinger et al. (2010) determined that of the 2,862 children that had complete information throughout the study, those who were exposed to nicotine prenatally were at

the greatest risk for behavioral problems at ten years of age. These risks were higher in children exposed to heavy prenatal tobacco exposure than in children exposed to light or no tobacco smoke. Interestingly, postnatal exposure was also associated with behavioral problems, but the results were much less significant. Yang et al. found similar results in their cohort of six and a half year-old children. Children exposed to prenatal smoking, maternal postnatal smoking, and/or paternal postnatal smoking had slightly lower IQ scores, as well as higher total cognitive difficulties and externalizing behaviors.

Multiple studies found an association between prenatal nicotine exposure and the development of ADHD. When controlling for confounding factors, Ellis et al. (2012) found that prenatal smoking predicted ADHD and oppositional defiant disorder (ODD) in four year-olds, as well as a comorbid diagnosis of the two. Ruckinger et al. (2010) supported this finding in their study of ten year-olds when they discovered that one of the strongest associations with abnormal behavior on the SDQ in children that were exposed to nicotine prenatally was hyperactivity/inattention. This is in line with previous research that has found greater abnormalities in externalizing behaviors in children prenatally exposed to tobacco smoke.

In the study by Motlagh et al. (2010), there was a high association between heavy maternal smoking and the development of ADHD. Severe maternal psychosocial stress was also found to be associated with this disorder. However, stress and heavy smoking were independently associated with ADHD, indicating that both factors may lead to this condition separately. These factors were associated with Tourette's Syndrome as well, but the findings were less significant. A conflicting study was conducted by Thapar et al. (cited in Tiesler & Heinrich, 2014) that compared the effects of maternal smoking on the

risk for ADHD in children who were genetically related and unrelated to the gestational carrier. The results showed that there was an increased risk for ADHD in those children who were genetically related, but no association in those who were carried by a surrogate.

Another study by Gaysina et al. (cited in Tiesler & Heinrich, 2014), focused on discovering whether or not a genetic component between prenatal alcohol exposure and conduct disorders/externalizing behaviors existed. Three different mother-child pairs were studied: those that were genetically related, children who were adopted at birth, and children who were adopted at conception. Regardless of genetics, children who were prenatally exposed to maternal smoking had a greater risk of developing conduct problems.

Lundberg et al. (2010), in their study of young conscripted Swedish males, discovered in the unadjusted analysis of prenatal smoking and intellectual performance that there was an increased risk for poor intellectual performance in male offspring of women who were moderate or heavy smokers during pregnancy. These results remained significant when adjusting for confounding factors, such as birth and parental characteristics. The sibling subset of this study revealed an increased risk for poor intellectual performance in both sons when the mother smoked during the first pregnancy, regardless of whether or not she smoked during the second pregnancy. But if she smoked only during the second pregnancy, neither son was at an increased risk for poor intellectual outcomes. Therefore, according to these results, prenatal smoke exposure does not influence intellectual performance. This suggests the influence of genetic/environmental factors in the development of intellectual deficits in children exposed to nicotine prenatally.

**Limitations**

As mentioned earlier, the assessment of prenatal alcohol exposure in these studies was primarily through maternal self report. With this type of retrospective data, there is always the possibility for inaccurate results due to faulty memory, fear of judgment, etc. Cope (2015) advocates for testing for cotinine, a metabolite of nicotine, in the urine or saliva instead of using maternal self report. However, these tests will only be positive if the woman has smoked within the past three days, making it necessary to use maternal self report to obtain more detailed data.

Another limitation of many of these studies was the inability to control for genetic and environmental factors. Ruckinger et al. (2010) and Yang et al. (2013) did not assess for parental psychological states and genetic factors. Similarly, Ellis et al. (2012) did not control for ADHD in the mother. Lundberg et al. (2010) were unable to control for maternal alcohol consumption, parental intellectual abilities, and behavioral problems. In addition, prenatal and postnatal smoke exposure were not distinguished.

None of these studies were longitudinal and Motlagh et al. (2010) had a small sample size. In the study by Ellis et al. (2012), the criteria for diagnosing psychiatric disorder was based on the past three months when six months is required for true diagnosis. Ruckinger et al. (2010) had a similar limitation. In their study, the SDQ was used to assess for behavioral problems. However, this tool is only used for screening purposes and is not diagnostic.

**Conclusion**

The results regarding the cognitive and behavioral effects of prenatal nicotine exposure in children are inconsistent. But despite the inability to establish a concrete

causal relationship, Tiesler & Heinrich (2014) state that the known effects of prenatal nicotine exposure should be enough to support the discontinuation of use. Longitudinal studies are needed in order to be able to assess the cognitive and behavioral states of the children throughout childhood.

### **Further Study**

The areas for future study regarding prenatal substance exposure and childhood development are many. For instance, numerous substances beyond alcohol and nicotine are used during pregnancy. Though the physical effects of these substances have been researched, there is a lack of information on varying types of prenatal exposures and their effects on language development and communication. In addition, language performance in fetal alcohol spectrum disorders over time and the effectiveness of interventions in this population requires supplementary data in order to make treatments more effective (Proven et al., 2014).

Another open area of study is the specific effect of environmental tobacco smoke (ETS) exposure on the developing fetus. Some research studies have attempted to take into account paternal smoking as a factor in nicotine exposure, but this factor is rarely isolated. Therefore, the results are often conflicting. For example, children exposed to nicotine prenatally are at a higher risk than the average child for developing ADHD. However, children whose mother was exposed to environmental tobacco smoke during pregnancy surprisingly have this same risk. ETS exposure is commonplace. Discovering new evidence regarding its lasting effects in prenatally exposed children may inspire awareness and lead to decreased exposure (Tiesler & Heinrich, 2014).



The outcome of maternal alcohol consumption on the infant while breastfeeding is a factor that is often omitted from studies, according to Dunney et al. (2015). This factor may be found in conjunction with prenatal alcohol use; however, the isolated effects of alcohol consumption during the breastfeeding period are unknown. Related to both prenatal alcohol and nicotine exposure, there is more information needed on the type and prevalence of internalizing disorders manifested in childhood. Tiesler & Heinrich (2014) reviewed some studies that supported the association of prenatal nicotine exposure with these disorders, while others found no association at all. Further study is needed to determine accurate correlation.

The above areas for future study are only a few of the countless areas in need of further research. The examples given were chosen because they were noted as gaps in the literature reviewed for this study or as important follow up questions necessary to build upon the current research.

### **Review**

The literature regarding the behavioral and cognitive effects of prenatal alcohol and nicotine exposure provides compelling associations with deficits in these areas. Though absolute causation has not been proven up to this point, the above research indicates that these substances present a great enough risk that they should be avoided during pregnancy.

Only a few of the studies in this review were longitudinal. In the future, it will be necessary to conduct a greater number of longitudinal studies that control for other factors that may interfere with behavior and cognition in children. However, because there are well known risks associated with consumption of these substances during

pregnancy, perhaps the focus should be on education of women and prevention of use during pregnancy. This would be the best possible way to avoid the cognitive and behavioral deficits in children that are most likely associated with prenatal use of alcohol and nicotine.

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**Appendix**

Table 1

<b>Study</b>	<b>Patient Characteristics</b>	<b>Instruments</b>	<b>Method</b>	<b>Results</b>	<b>Limitations</b>
1) Coles, 2011	-Children with FASD		<p>-Factors to take into consideration: Evidence for prenatal alcohol exposure, caregiving environment, comorbidities, and differential diagnosis</p>	<p>-Mean IQ of around 70 -Damage to the central and peripheral nervous systems resulting in fine and gross motor delays, affecting balance and motor control -Visual-spatial deficits, indicated by problems in these areas: handwriting, clumsiness, and mathematics -Deficits in executive functioning, such as in active working memory, planning, problem solving, and organization -Difficulties in regulating arousal and in self-control, often manifesting as ADHD</p>	<p>-At present, there is no way to determine whether comorbidities, such as ADHD, depression, etc., are the direct results of prenatal alcohol exposure or if they are due to a combination of genetics, environment, etc.</p>

<p>2) Comasco et al., 2012</p>	<p>-2264 mother-child pairs -Swedish antenatal clinic</p>	<p>-The AUDIT alcohol consumption self-report tool</p>	<p>-Statistical significance <math>p &lt; 0.05</math> -Alcohol biomarker blood tests (CDT and PEth) -Longitudinal study</p>	<p>-229 of 1868 women admitted to consuming alcohol during pregnancy, ranging from monthly to multiple times a week -Nicotine use before and/or during pregnancy was positively correlated with those who drank during pregnancy -Babies born to women who drank during pregnancy had a higher birthweight (3,665 g vs. 3,518 g)</p>	<p>-Only 1868 women participated at second follow-up, which was at 32 weeks' gestation -Response bias must be taken into account, as alcohol consumption was self-reported -9% of the women who were invited to participate declined</p>
<p>3) Dorrie et al., 2014</p>	<p>-Children exposed to alcohol prenatally</p>			<p>-Reduced head circumference, prevalence of epileptic seizures, growth deficits, corpus callosum abnormalities which may lead to impaired verbal learning ability, basal ganglia volume reduction possibly resulting in lower IQ scores</p>	<p>-There is no long-term data on FASD outcome beyond the age of 30</p>



<p>4) Dunney et al., 2015</p>	<p>-Cohort study of 907 women -Dublin, Ireland -2010-2011</p>	<p>-The questionnaire used was developed from the AUDIT-C and the T-ACE survey tools.</p>	<p>-Data analysis with the Statistical Package for Social Sciences (SPSS) -95% confidence intervals</p>	<p>-Alcohol consumption was positively correlated with older age (35-39), private health care, Irish nationality, cigarette use, and a history of illicit drug use.</p>	<p>-The possibly for underreporting of prenatal alcohol consumption due to self-reporting -There was a loss of participants</p>
<p>5) Graham et al., 2013</p>	<p>- 272 children, between the ages of 8 and 16, and their caregivers -Participants were recruited from five different sites across the U.S.</p>	<p>-The Child Behavior Checklist (CBCL) parental questionnaire -The SCT parental questionnaire</p>	<p>-Data analyzed using the SPSS</p>	<p>-The alcohol exposed groups showed significant elevations in SCT. However, the children who were exposed to alcohol but did not have ADHD had significantly lower SCT scores compared to those who had ADHD.</p>	<p>-The number of children in each category was different. -IQ was not controlled for in this study.</p>
<p>6) Jacobson et al., 2013</p>	<p>-Children with FASD, followed into adulthood</p>	<p>-126-item Achenbach Adult Self-Report</p>	<p>-Maternal self-report of alcohol consumption validated by recognized cognitive defects and alcohol metabolites in meconium samples</p>	<p>-The effects of prenatal alcohol exposure are permanent and continue into adulthood -Concentrated levels of alcohol, such as multiple drinks on one occasion, as opposed to one drink on different occasions, are thought to have a</p>	

				greater effect on the fetus, but in this study there was just as much of an effect in those who were consistent drinkers	
7) Mattson & Riley, 2011	-Children who have no physical characteristics of prenatal alcohol exposure		-Two main ways of determining prenatal alcohol exposure: maternal report, prospectively or retrospectively, or a dysmorphology examination	-Compared to other children with similar traits (such as low IQ), the alcohol-exposed children experienced impairment in externalizing behavior, adaptive skills, and verbal learning. -When comparing alcohol-exposed children with ADHD with other children with ADHD, alcohol-exposed children had greater impairments related to visual-spatial reasoning, problem solving, flexibility, as well as encoding and shift aspects of attention.	-The studies that have been done have each only focused on one aspect of the alcohol phenotype. It is not possible for one study to simultaneously account for every aspect. -Environmental, genetic, or other factors may interact with the fact of alcohol exposure, therefore creating the possibility for more profiles.
8) Pei et al., 2011	-Children with comorbid FASD and		-Computer-based literature review of	-As compared with other symptoms of FASD,	-Sample sizes are often small

	mental health issues		peer-reviewed journals and book chapters	psychiatric symptoms tend to persist into adulthood and may increase -Prevalence of FASD in the US is 9-10 in every 1000 births	-More research needed relating these findings to environmental protective factors
9) Peles et al., 2014	-108 pregnant women at gestational week less than or equal to 30 weeks -Hebrew-speaking women presenting to a hospital in Israel -They were recruited because they presented to the hospital with medical complications	-Questionnaires used include AUDIT C and TWEAK for alcohol use, Fagerstrom for nicotine exposure, and the addiction severity index (ASI) for other substance use	-These women were interviewed to determine exposure to alcohol, nicotine, and/or psychoactive substances. Those who were exposed were given the opportunity to participate in a Brief Intervention (BI). 46 of the 108 were exposed and 41 participated in the BI.	-As a result of the BI, self-report of exposure was reduced for the duration of the pregnancy, but then increased after birth.	-The association of the studied group with a lesser amount of education may be related to poor lifestyles and health habits, leading to the medical conditions that brought them in – this was not a part of the study
10) Proven et al., 2014	-124 school-aged children with a clinical diagnosis of FASD – ages 5-18	-CELF-4 language test	-Data analyzed using SPSS, level of significance of $p < 0.05$	-Poor performance across the board related to both expressive and receptive language abilities -Almost 70% scored a rating of “severe” on the	-No children with FAS were included -The CELF-4 has not been used much to date for research analysis purposes

				Core Language Index, indicating communication impairments	-Co-morbid diagnoses and environment were not analyzed in this study
11) Robinson et al., 2010	-2868 pregnancies between 1989-1991 with a 14-year follow up of the children between 2003 and 2006 – 1860 participated all the way through -Obstetric hospital in Western Australia	-The CBCL parental questionnaire -For reporting their level of alcohol intake, the women were given five categories to choose from: no drinking, occasional, light, moderate, and heavy.	-Longitudinal regression models used	-Light and moderate drinking at 18 weeks showed a decrease in CBCL scores, indicating better behavior -Heavy drinking was associated with higher CBCL scores = poorer behavior -Fewer behavioral problems were noted over the 14 years in children whose mothers were light drinkers (2-6 standard drinks per week) during their first trimester than in children whose mothers did not drink at all	-Because weekly drinking was averaged, there was no way to test for binge drinking episodes, therefore specific patterns of drinking could not be assessed.
12) Warren et al., 2011	-Neonates and children with FASD			-MRI technology is being used to track brain changes in people exposed to alcohol	-Dysmorphic features are sometimes subtle and therefore underreported.

				prenatally, which has enabled discoveries related to specific areas of the brain and how they respond to alcohol exposure.	Computer recognition of these features is being developed.
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Table 2

Study	Patient Characteristics	Instruments	Method	Results	Limitations
1) Cope, 2015	-Women who smoked during pregnancy and their fetuses			-Damage to the fetus: intrauterine growth retardation, altered gene expression leading to an increased risk of neural tube defects, decreased pulmonary function possibly leading to asthma in children, impairment of neurological development, increased risk of colic	-Testing needs to be biological since self-report is often inaccurate.
2) Ellis et al., 2012	-4 year-old children in Trondheim, Norway -All children born in 2003-2004 and their parents were invited to participate-995 participated all the way through	-Preschool Age Psychiatric Assessment -The SDQ parental questionnaire	-Semi-structured diagnostic interview	-When controlling for confounding factors, prenatal smoking predicted ADHD and ODD in 4 year-olds, as well as a comorbid diagnosis.	-Did not control for ADHD in the mother -Retrospective study requiring information from four years prior -Criteria for diagnosing disorders was based on the past three months when

					six months is required for a true diagnosis
3) Lundberg et al., 2010	-172,182 conscripted Swedish males (around 18 years of age) born to Nordic mothers, with 14,722 of these males being sibling pairs	-Intellectual performance tested in four dimensions: logical/inductive, verbal, spatial, and theoretical/ technical.	-Proc Genmod in SAS with 95% confidence intervals	-According to this study, prenatal smoke exposure does not influence intellectual performance.	-Prenatal and postnatal smoke exposure were not distinguished -Inability to control for maternal alcohol consumption, parental intellectual abilities and behavioral problems
4) Mei-Dan et al., 2015	-Montreal, Quebec, Canada -Women who gave birth from 2001-2007 -20,938 deliveries, 1646 to smoking mothers			-Higher rates of adverse outcomes (compared to non-smoking women) were also seen in women who only smoked five or less cigarettes per day	-This is a retrospective study
5) Motlagh et al., 2010	-222 children between 7 and 18 with either ADHD, Tourette's, both conditions, or neither condition		-Cognitive ability and mental health were assessed via different rating scales	-Independent association of heavy maternal smoking and severe maternal psychosocial stress and the development of ADHD.	-Much of the data collected about the pre- and perinatal history was based upon maternal self-report -Small sample size

<p>6) Ruckinger et al., 2010</p>	<p>-5,991 children and their parents from Munich and Wesel Germany, born between 1995-1998</p>	<p>-The SDQ parental questionnaire</p>	<p>-Poisson regression models were used to obtain relative risk estimates -Data analyzed from the German Infant Nutritional Intervention (GINI), an ongoing birth cohort study</p>	<p>-Of the 2,862 children that had complete information throughout the study, those who were exposed to tobacco prenatally were at the greatest risk for behavioral problems at 10 years of age.</p>	<p>-The SDQ is used for screening. It is not diagnostic. -This study did not confound for parental psychological problems. -Information based upon maternal self-report</p>
<p>7) Tiesler &amp; Heinrich, 2014</p>	<p>-Children who were prenatally exposed to nicotine</p>		<p>-Detection of nicotine exposure: retrospective or prospective maternal report, nicotine or its metabolites, such as cotinine in urine, cord serum, meconium, amniotic fluid, hair, nails</p>	<p>-ADHD, with hyperactivity or inattention: children exposed to nicotine prenatally are at a higher risk for developing this disorder, but so are children whose mother was exposed to ETS during pregnancy -Regardless of genetics, children who were exposed prenatally to maternal smoking had a greater</p>	<p>-Results are conflicting regarding the effects of ETS exposure</p>



				risk of developing conduct problems.	
8) Yang et al., 2013	-A cohort of Belarusian children around 6.5 years of age who were either exposed prenatally to maternal smoking or exposed postnatally to maternal or paternal smoking	-The Weschler Abbreviated Skills of Intelligence (WASI) -The SDQ parental questionnaire	-Cluster-adjusted multivariable regression	-Children exposed to prenatal smoking, maternal postnatal smoking, and/or paternal postnatal smoking had slightly lower IQ scores, as well as higher total difficulties and externalizing behaviors.	-This study did not assess parental psychological states and genetic factors. -There is always the possibility for underreporting of maternal smoking, especially due to prenatal smoking prevalence in the studied population being lower than the national average

