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Nicotine Exposure During Pregnancy and Risk of Behavioral Disorders in Offspring

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Abstract

Background: Smoking during pregnancy has been linked to various health outcomes in offspring. The relationship between nicotine (smoke) exposure during pregnancy and behavioral disorders, such as attention deficit hyperactivity disorder (ADHD), has been studied for years yielding mixed results. These studies have varied in quality of design and methods, alluding to varied association conclusions. The purpose of this summative review is to determine the association between prenatal nicotine exposure and risk of developing behavioral disorders, such as ADHD.

Methods: A systematic search using Lindell Library and PubMed was used to find peer-reviewed studies on the topics of maternal nicotine exposure during pregnancy, and smoking during pregnancy and behavioral disorders in offspring. Specific areas of interest included maternal smoking during pregnancy and ADHD, nicotine exposure during pregnancy and effects on offspring, and ADHD.

Results: Several large sample studies indicate there is a correlation between nicotine exposure in utero and ADHD in offspring. However, a few smaller, single population or regional studies fail to confirm the relationship. This indicates more research needs to be conducted.

Conclusions: More research needs to be done on the topic, particularly prospectively, while addressing confounding variables. More recent research using various forms of nicotine exposure, such as vaping or e-cigarette use, needs to be done using a large-scale study in various populations to examine the possible associated risks. Smoking during pregnancy is still not recommended, in any form, because of the known poor health outcomes for mother and baby, and possible associated risks of behavioral disorders.

Introduction

Prenatal health issues have been studied for decades, in an attempt to prevent harm or health problems for the growing fetus. Many pregnant women are given guidelines to follow regarding the safety of their baby, including but not limited to diet restrictions, exercise limitations, as well as environmental exposure awareness. Smoking exposure questionnaires are often included in prenatal visits across the US, as well as other developed countries, because of the increased maternal and fetal risks associated with the exposure. Smoking exposure is not only limited to cigarettes, but also includes e-cigarettes or vaping with nicotine, secondhand smoke exposure, and questionably nicotine exposure from resources such as nicotine replacement patches.

When a pregnant woman attends her first prenatal visit, the American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women that are using nicotine products, including those listed above, are given education about smoking cessation, and motivational quit plans.[1] The ACOG stands by this recommendation due to the known risks associated with nicotine/ smoking exposures, including low birth weight, childhood obesity, orofacial clefts, preterm labor, and placenta previa or abruption, just to name a few.[1] However, not included in their list is a continued study association between maternal nicotine exposure and risks of developing behavioral disorders, such as Attention Deficit Hyperactivity Disorder, or ADHD. "Indeed prenatal smoke exposure has been associated with the full range of externalizing behaviors, including the propensity of the offspring to abuse later in life".[2] The reality that these potential risks could have lifelong sequelae presents a prenatal health issue needing to be addressed.

ADHD is a persistent and developmentally inappropriate pattern of inattention, hyperactivity, and or impulsivity.[3] Children with ADHD may have disruptive behaviors, such as failing to

remain seated, talking excessively, playing noisily, and blurting out answers before questions have been completed.[3] According to an article by Matza et al., the US alone, the prevalence is between 4% to 12%, and the percentage of children being treated for ADHD dramatically increased from the 1980s to the 1990s.[3] Having ADHD can affect a child's academic performance, social functioning, and overall quality of life.[3] According to a review study on the economic burden of the disorder, it was found that the financial burden to families of having this disorder were on average equal to or higher than those diagnosed with asthma (another common diagnosis in childhood).[3] One study found that in 2004, children with ADHD had an average treatment cost for 3 years was $4891, compared to $221 for child patients with no psychiatric disorder.[3] Patients with ADHD have on average a higher number of hospitalizations, primary care visits, and pharmacy fills. Not only is the diagnosis tied to a financial burden on families, but also presents an emotional burden as well. It is linked to strain on the parent-child relationship, affecting parent's marital functioning, and higher parental stress.[3]

However, ADHD does not disappear in childhood, the impact of ADHD continues into adulthood. It is estimated that 30-70% of children with ADHD continue to have symptoms into adulthood.[3] These adults typically have issues with organization and distractibility, and are also tied to many negative outcomes, including higher rates of criminality, poor job performance, lower occupational status, issues with social skills, and poor driving records.[3] Adults with ADHD also have, on average, two to three times higher annual cost of medical care compared to those who don't.[3]

Discussing the consequences of these behavioral disorders, such as ADHD, in a lifelong manner highlight the importance of acknowledging their risk existence in terms of public health and why we need to address the topic. Although this has been studied for decades, with a rise in the

number of diagnoses in childhood, and more alternative forms of nicotine being used, such as vape pens or e-cigarettes, there continues to be studies on the topic and should be used to inform expecting women of the associated risk, if the association is found to be valid.

The goal of this paper is to establish if there is an increased risk of ADHD when exposed to nicotine in utero. The diagnosis of ADHD in a patient previously exposed to nicotine in utero, as well as animal studies that analyzed characteristics consistent with ADHD after being exposed to nicotine in utero, were used as measured outcomes. To determine this, various literature reviews and peer-reviewed scientific studies will be used collectively, and the data can be used to help with recommendations regarding prenatal health and safety. The limitations of this topic are largely the types of studies utilized, and the longevity of the study needed in order to relate the two. Another major limitation is confounding variables, such as other environmental exposures between birth and age of diagnosis, as well as genetics, and diagnostic criteria.

The objectives of this paper are to identify nicotine containing sources that pregnant women are using or are exposed to, explain how nicotine affects the fetus in utero, the biological development that may be altered by nicotine exposure and how that relates to the development of behavioral disorders, and present the various etiologies and research of ADHD. This is a summative review paper using peer reviewed scientific articles and studies, as well as clinically backed practices being used today in the US, in an attempt to test the hypothesis that nicotine exposure during pregnancy increases the risk of developing ADHD.

Background: Literature Review

Prevalence of Smoking During Pregnancy

According to the Center for Disease Control, “one in 14 women who gave birth in the US in 2016 reported smoking during pregnancy”.[4] Expecting mothers age 20-24 were the most likely

to smoke, where they found 10.7% of women in that age group admitted to smoking at some point throughout their pregnancy.[4] They also noted that smoking during pregnancy was least prevalent in women of higher education, including master's degree or higher.[4] Interestingly, European birth cohorts report a much higher rate of smoking, with a prevalence between 14% and 38% across Europe.[5] There is an overall decreasing prevalence of smoking during pregnancy in developed countries and possibly increasing prevalence in developing countries. Almost one fourth of the population of pregnant women in developing countries continue to smoke while pregnant, proving nicotine exposure is a health issue worldwide.[5]

Nicotine Content and Forms of Nicotine Containing Products

Smoking during pregnancy has widely been inclusive of tobacco cigarettes, however, more recently there has been question about nicotine exposure through other forms of smoking, such as vaping, or even nicotine replacement patches. According to Taghavi et al., the average amount of nicotine in domestic cigarettes is about 6.17 to 12.65 mg of nicotine, based on varying amounts of tobacco in different brands and each cigarette.[6] The amount of nicotine in E-cigarette liquids is widely variable, and often questioned, even with what is labeled on the container. Some liquids contain 0 mg of nicotine, while others have 87.2 mg/ml or more.[6] The lack of consistency regarding labeling, chemistry, and approval largely presents an issue with this form.

There is no Food and Drug Administration (FDA) approval for the use of vaping devices in any form, for any purpose. Until August of 2016, there was no FDA or major governing force regulating the use or creation of vaping products, and there was largely an unknown amount of various chemicals, including nicotine, in each sample sold.[7] For example, if there was a sample that claimed to have 0 mg of nicotine, there was no regulation or legal testing done on the sample

to confirm the lack of presence or use of nicotine in the product, and people using those samples were under the assumption that they were using nicotine free products, when there were really largely varied amounts within each vile. Since the FDA has been granted authority for more regulation, many retailers have been shut down, due to lack of consistency or false product labeling.[7] Although they are more regulated, they are still not approved, and the use of such devices are still not recommended , particularly for pregnant women.

One study compared the use of different powers of e-cigarettes, as well as different brands, to the use of combustible cigarettes.[8] They found that overall, the use of a 5.7W e-cigarette, which is considered on the low end of power, the amount of nicotine per puff was on average less than that of the combustible cigarette.[8] However, they also noted that with combustible cigarettes, the average nicotine amount per puff increased as the time the cigarettes burned was increased. Therefore, as it combusts more, the tobacco was seemingly more dense and released more nicotine, whereas with the e-cigarette, there was no variance with the amount of nicotine per puff with the length of use, per smoking session. Regarding the e-cigarette, they also found that the amount of nicotine per puff was largely influenced by the wattage used, and had a direct relationship, increasing in quantity as the wattage increased when they used an average nicotine concentration liquid.[8]

With the use of vaping devices being recommended against during pregnancy, other forms of nicotine containing products, such as nicotine replacement therapy (NRT) needs to be addressed for potential risk as well. People use NRT, in forms of gum, patches, sprays, and lozenges, as a method of quitting smoking. According to the American Cancer Society, nicotine in NRT is meant to match the amount of nicotine you get from tobacco, just without the other harmful products. “You should get a nicotine dose fairly close to what you’ve been getting”.[9] This

presents an issue, as the effects of nicotine use during pregnancy and the risk of associated neurodevelopmental sequelae are being studied. Because of this exposure risk, it is recommended that pregnant women that smoke 5 cigarettes per day or less use strictly behavioral support to assist in quitting smoking, instead of NRT, and those that smoke more than 5 per day to use a combination of NRT and cognitive behavioral therapy to guide quitting, using the lowest dose possible for NRT to minimize nicotine exposure.[10]

Tiesler and Heinrich's summative review discusses how nicotine is a chemical compound that is considered an alkaloid, that is often found in tobacco products and nicotine replacement products.[5] Once nicotine is absorbed into the system and in the bloodstream, it can affect many different parts of the body, including the brain, lungs, and liver. In the liver, it is metabolized and then excreted through urine. Unfortunately, like many toxic substances, nicotine's metabolite, cotinine, can cross the placenta and go into fetal circulation. When metabolite levels were tested in mothers that were directly or passively exposed to smoke, or nicotine during the first trimester of pregnancy, there was already a presence shown by an accumulation effect of metabolite concentration in the amniotic fluid and fetal serum.[5] Once nicotine is exposed to the fetus, it can largely effect their neurological development, as well as their physical growth.

What Does Nicotine Do To The Body?

Nicotine is a major teratogenic component of tobacco, and affects the body by modulating neurotransmitter release, gene expression, neuronal outgrowth, cell survival, and synapse formation and maturation.[11] To better understand the possible association between nicotine and the development of behavioral disorders, such as ADHD, research has been done in various studies on rats examining the physiology of nicotine on the body. Studies done on animals, such as mice and rats, that report behavioral alterations, parallel those seen in maternal smoking in

humans, and therefore are used to study direct effects on identified genetic markers.

A study done by Balsevich et al. states that nicotine interferes with the developmental time course of normal brain development resulting in structural and behavioral alterations. The striatum plays a central role in many nicotine-related phenotypes, such as motor function, negative emotion, and aspects of learning and memory, and this study analyzes the effects of nicotine on the striatum as a structure.[12] The study suggests those with prenatal nicotine exposure had a decreased striatal volume, and decreased striatal neuronal numbers compared to those without nicotine exposure. Balsevich et al. concluded that "nicotine exposure exerts immediate structural changes and a gradual development of behavioral abnormalities", and fetuses with nicotine exposure also had an increased hyperactivity reaction to nicotine, indicating a gene-by-environment reaction.[12]

According to Buck et al., a Colorado study done on mice that examined the association of maternal smoking during pregnancy, a form of developmental nicotine exposure, found an increased risk of ADHD, throughout the first and second generations of mice that were exposed to nicotine prior to and throughout the breeding process.[13] They found that nicotine leads to altered expression and dysfunction of nicotinic acetylcholine receptors (nAChRs), hypersensitivity to nicotine-induced nAChR mediated dopamine release, and impaired dopamine transporter function in developmental nicotine exposure (DNE) mice.[13] They also conclude that "DNE enhances nicotine preference, elicits hyperactivity and risk- taking behaviors, perturbs the rhythmicity of activity, alters nAChR expression and function, impairs DAT function, and causes DNA hypomethylation in striatum and frontal cortex of both first and second- generation adolescent offspring".[13] From their studies on mice, analyzing the physiology of nicotine on the body, it is demonstrated how nicotine can directly impair normal neurodevelopmental processes,

and therefore lead to sequelae such as ADHD, and risk taking behaviors.[13]

A study conducted by Schneider et al. finds that prenatal nicotine exposure causes alterations in the development of neurochemical markers for dopamine in offspring.[11] There was found to be a significant increase in the expression of the DRD5 mRNA in the striatum of animals prenatally exposed to nicotine,[11] indicating a direct genetic effect. They discuss that the most direct effects of prenatal nicotine exposure is on the nicotinic acetylcholine systems.[11] However, since there is a close anatomic association of the acetylcholine and dopamine (DA) systems, it is likely to have secondary effects on the dopamine system as well. They found that nicotine caused a dysregulation of dopamine signaling, implicating deficits of attention and impulsive responding,[11] which is part of the diagnosis of ADHD. They also found that prenatal exposure to nicotine has lasting effects on behaviors regulated by dopamine, including locomotor activity, also an indicative core element of ADHD. To study the genetic effects further, they analyzed the lasting effects of prenatal exposure on quantitative expression of the dopamine related genes that index DA regulatory function or have been associated with ADHD. Their results show that there was an associated effect on specific genes, particularly the DRD5 allele, which was shown to have a correlation to lower scores on performance tests,[11] which is also a characteristic trait of those with ADHD. The analysis of prenatal nicotine exposure results demonstrated that compared to the control, those that were exposed to nicotine in utero did not have a change in number of offspring, or number of dead or malformed offspring, but it did show lower birth weight in those exposed.[11] Their study highlights the genetic effects of nicotine exposure, while also addressing the concern that these genetic changes may lead to higher rates of fetal mortality. However, they confirmed that it doesn't statistically alter mortality rates, but rather infant size and number full term births, which is a known risk of nicotine exposure while pregnant.

Along with the genetic effects of nicotine exposure, there may be measurable, physical changes that result from exposure that can play a role in the neurodevelopmental process. A study done by Zeeuw et al. compared children that were diagnosed with ADHD that were exposed to nicotine in utero to those with ADHD that were not exposed, and compared brain volumes. They found that those with ADHD that were exposed to nicotine had the smallest brain volumes, and those with ADHD without exposure had intermediate size, compared to a brain of a child without ADHD and unexposed with the largest size.[14] This indicates that any nicotine exposure decreases brain volume size, particularly in the cerebellar region.[14] People diagnosed with ADHD tend to have increased locomotor activity, lower academic performance, and impulsivity, and these may questionably be attributed to their decreased brain size, and even more so, noted with in utero nicotine exposure.

Maternal versus Paternal Biological Effects of Nicotine Exposure

There is also some discussion on whether the effects of tobacco and nicotine are solely due to maternal smoking, or if it also is affected by men smoking as well. In general, more men smoke than women do, but when it comes to pregnancy, more women are scrutinized for their actions, and there is little to no judgement on the father's smoking status.[15] Results from a study done on mice, where male mice were exposed to nicotine and bred with drug-naive females, concluded that the offspring demonstrated increased spontaneous locomotor activity and significant deficits in attention, brain monoamine content, dopamine receptor mRNA expression, and reversal learning.[15] "We have found that nicotine exposure of male mice produces behavioral changes in multiple generations of descendents".[15] This indicates that there is a DNA change that occurs due to nicotine, particularly analyzing their data that suggests it is due to spermatozoal DNA methylation that allows for transgenerational phenotype transmission.[15] These changes may not

be due to direct maternal nicotine use, but rather exposure to nicotine in the perinatal period between the mother and father. Therefore, fathers who smoke should be educated, as well as screened, during prenatal visits, due to their potential genetic effects of smoke exposure.

ADHD and Nicotine Exposure

ADHD is characterized by having inappropriate and impairing levels of inattentive, hyperactive, and impulsive behaviors that affects about 5% of children and persists into adulthood in about 65% of cases.[11] ADHD is diagnosed through a several step process that has no single test to confirm diagnosis. According to the Center for Disease control, ADHD is diagnosed by healthcare providers, while following criteria from the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5).[16] In order to be diagnosed with ADHD, a person has to show a persistent pattern of inattention and or hyperactivity-impulsivity that interferes with functioning or development.[16] Based on CDC statistics, approximately 6.1 million children are diagnosed with ADHD each year in the US, majority of which are aged 6-11 years old, and boys are more than twice as likely to be diagnosed than girls.[17] Since 2003, there has been a nearly 2 million per year case increase in children diagnosed with ADHD, and many of them have additional mental or behavioral disorders, such as conduct disorder or anxiety.[17] Although there is a large heritability factor for ADHD, recent studies have shown that a rare number of variants were found to be over represented in ADHD cases compared to controls, indicating neurodevelopmental processes in the etiology of ADHD,[12] such as nicotine exposure. Sciberras et al. states that an estimated 10-40% of the variance in etiology of ADHD is likely to be accounted for by environmental factors.[18]

Alkalm et al. states they have previously shown that prenatal nicotine exposure (PNE) induces cognitive behavioral deficits in offspring and decreases the contents of dopamine and its turnover

in the prefrontal cortex in mice.[19] It is known that one of the core factors in the pathophysiology of ADHD is the dysfunction of the dopaminergic system in the brain.[19] PNE reduces the release of dopamine in the medial prefrontal cortex, and induced behavioral deficits in cliff avoidance, object based attention, and sensorimotor gaiting in offspring in mice. These findings would be indicative of behavioral changes consistent with changes found with ADHD. PNE disrupts the dopaminergic (DAergic) system and induces neurobehavioral abnormalities in mouse offspring.[19] According to Alkam et al., nicotine in maternal blood can easily cross the placenta and interact with the nAChRs in the fetal brain, which appear as early as gestational day 12 in rats and mice, and this can largely affect cell signal transducers for cell proliferation and differentiation during the early stages of nervous system development.[19] Their study states that nicotine binds to the nAChRs in the fetal brain and affects the timing and intensity of critical neurotransmitter signals that are needed for normal development of many neural structures and circuits in the developing brain, and influence behavioral abnormalities later in life.[19] A summative review by Neuman et al. discusses their attempt to establish a biological mechanism for ADHD, and how it relates to genetic polymorphisms in the dopaminergic system.[20] Considering specific loci, particularly in the cortical and striatal regions, there appears to be an increased dopamine release due to stimulation of high affinity neuronal nicotinic acetylcholine receptors. Because of this, a child's specific genotype in these specific loci may need to be considered.[20] Developing a foundation to better understand the direct biological effects of nicotine on the body and how those changes are associated with the development of ADHD is a vital component to apply to the most recent data, and needs to be considered when designing future research studies.

Although results varied between studies regarding direct effects of nicotine exposure in utero and

risks of neurodevelopmental disorders, such as ADHD, many studies found a statistically significant association between the two. A study by Schnieder et al. used rats to compare prenatal nicotine exposed rats to control groups. They found that those that were exposed had increased variability of response times for correct responses to given tasks, that negatively correlated with accuracy, and positively correlated with anticipation,[11] which are characteristics consistent with ADHD.

The association between the two is also supported by many other studies completed.[2,19,21-25] "Prenatal smoking represents an important risk factor for ADHD", Joelsson et al. states, "the study supports previous findings of association between smoking during pregnancy and offspring ADHD".[21] In future studies utilization of biological markers of smoking, such as cotinine levels, would confirm the present results",[21] which is what Tiesler and Heinrich's study utilized.[5] According to Figure 3, smoking during pregnancy increases the risk of having ADHD, but also statistically significantly increases the risk of having other neurodevelopmental disorders as well, noting an adjusted OR of 1.59 for ADHD alone, including the highest portion of the sample size.[21]

Some other rather large studies have also concluded that there is an association between smoking during pregnancy and increased risks for ADHD. A study was completed in Australia with over 66,000 participants, that considered maternal smoking during pregnancy, as well as maternal criminal record. They discovered that smoking during pregnancy and maternal offending [of 2 or more crimes] were separately and together associated with increased risk of developmental vulnerabilities, even so after adjusting for familial or other prenatal risk factors.[22]

A summative review by Neuman et al. revealed that the "average number of [ADHD] symptoms was significantly higher in the offspring who were exposed to prenatal smoking than in those

who were not, with a p value of 0.006".[20] Likewise, the same pattern was found for the nine symptoms of inattention and of hyperactivity-impulsivity through a very extensive twins study.[20] They also found that the average symptom counts [of ADHD] were significantly higher in subjects with smoke exposure than those who were not and there was also an increased number of risk alleles in those subjects.[20] This indicates not only a mechanism of action, but also a strong outcome statistically relating the two. Figure 1 shows the different genotypes studied comparing prenatal smoke exposure to those without it, and the mean number of ADHD symptoms per the diagnostic criteria. Using a sample size of 1540 twins to compare sets of expressed alleles, the results establish a statistically significant difference between the smoke exposure and the control (no smoke exposure in utero). There are an increased number of alleles expressed in those that were exposed compared to those that were not.[20] People with ADHD have been found to have an increased number of these particular alleles studied. If nicotine causes an increased expression of that specific allele, it indicates a causation effect.

Animal Studies

Using animal studies in conjunction with human studies is an important tool, specifically in this topic, because a vast majority of the confounding variables can be better controlled in animal studies than they can be with human samples, which helps isolate specific aspects of the research. "Animal studies report behavioral alterations from pre and early post-natal nicotine exposure that parallels those seen with maternal smoking in humans. Therefore, animal models provide a useful tool in which to examine the behavioral effects of pre- and post-natal nicotine, specifically locomotor activity, anxiety- like behavior, and selective learning and memory processes"[12] which parallel the characteristics of ADHD.

An interesting study was conducted on rats and mice to determine the direct effects of nicotine

exposure during pregnancy on dopamine (DA) release, as a potential biological pathway connecting the two. They found that nicotine exposure in utero is significantly related to ADHD, even with potential confounds taken into account.[19] They demonstrate that nicotine exposure in utero reduces the turnover of DA in the prefrontal cortex, due to impaired extracellular release in that area. They stimulated the cells in these specific areas using potassium in order to determine if the cells that are exposed to nicotine are lacking in DA release. What they discovered was those cells that were not stimulated had a statistically significant decrease in the amount of extracellular DA, compared to those that were stimulated or the control group.[19] This indicates that nicotine prevents the release of DA in normal amounts, which can lead to attention deficits and impulsive behaviors.

Second Hand Smoke Exposure

Throughout these studies, most often they include direct maternal smoking or nicotine exposure during pregnancy. A study done by Gatzke-Kopp and Beauchaine was the first to examine the effects of secondhand smoke exposure. They used self-reporting from parents during the study and put a scale to quantify smoking exposure, either directly or indirectly.[2] They found that both the smoking group and the second hand exposure group had significantly higher ADHD scores than the non-smoking group, comparatively ($p < 0.005$), and the smoking group did not statistically differ from the second hand exposure group.[2] "Children exposed to cigarette smoke, regardless of whether or not the exposure was direct or second hand, showed more severe symptoms of ADHD",[2] they concluded.

Kovess et al. studied the effects of maternal and paternal smoking association with risk of ADHD, so not to only include maternal smoking habits in the perinatal period, but paternal as well. There was found to be a probable association between maternal smoking and ADHD

development (OR: 1.45) and paternal (OR: 1.17), demonstrating that maternal smoking associations to ADHD is stronger than that of paternal prenatal smoking risks.[23] Interestingly, there was a significant increased risk when mother and father both smoked during the prenatal period, compared to either of them alone, with an odds ratio of 2.06.[23] When both parents are smoking in the prenatal period, it is assumed that there is an increased nicotine exposure. Subsequently, these studies present confounding factors when attempting to establish a relationship between the two variables. For example, if the potentially higher risk of developing ADHD is due to the nicotine directly, or rather the other toxins in cigarette smoke that the fetus is potentially being exposed to. Studies need to analyze and critique other effects, such as income, parental antisocial behavior, prematurity, birth weight and poor parenting practices. Gatzke-Kopp and Beauchaine found that smoke exposure during pregnancy predicted conduct disorder symptoms and other behavioral disorders over and above the prior mentioned.[2] In their analysis, smoking exposure was the only variable to yield a significant coefficient. Figure 4 demonstrates their variables and associated p values, showing that smoking exposure was the only statistically significant value at predicting ADHD behavior or symptoms.[2] Additionally, Biederman et al. found that "maternal smoking during pregnancy was associated with a significantly increased risk for ADHD independently of conduct disorder".[24] Although smoking was the only statistically significant variable to predict ADHD, other variables such as stress during pregnancy, are often thought to be associated.

Other Variables and Future Habits

Rodriguez and Bohlin claim that smoking during pregnancy is independently associated with development of ADHD, and also studied stress during pregnancy as an independent variable, as the two are often correlated.[26] A similar study was conducted by Ellis et al. that had comparable

results. They accounted for parental anxiety, depression, personality disorders, drug abuse, and socio-economic characteristics.[27] After adjusting for those confounding variables, they concluded that smoking during pregnancy (SDP) was found to increase the odds of ADHD by more than 2.5 times ($p<0.001$), as shown in Figure 2.[27] Vuijk et al. 's findings support this conclusion, as well. They found through their studies accounting for several confounding variables, such as socioeconomic status, maternal psychopathology, harsh parenting practices, as well as the mother's use of alcohol during pregnancy, and even so that although genetics and environmental risks account for much of the development of ADHD, "prenatal smoking still uniquely predicted offspring ADHD symptoms, as well as conduct problems".[28] Their research shows that prenatal smoking has a lasting influence on a child's structural and functional development.[28]

Gard et al. conducted a study on all girls to determine the association in a longitudinal, all girls study.[29] They too accounted for some common key confounding variables, similar to those of Vuijk. Their studies show that "compared to girls whose mothers did not smoke during pregnancy, girls with mothers that did smoke were of significantly lower socioeconomic status, reported less substance use in adolescents and had greater maternal and teacher reported symptoms of behavioral disorders" (p value <0.001).[29]

Similarly, Vuijk et al. conducted a study on school age children and found that "prenatally exposed children had higher ADHD symptoms scores",[28] and continued, "prenatally exposed children are most prone to follow a path of high levels of ADHD symptoms and associated elevated risk for early onset experimentation with smoking".[28] Interestingly, their study focused on the ability to predict intervention failure in elementary schoolchildren with disruptive behaviors. They concluded that those children who had prenatal smoke exposure were not

affected by interventions to alter their course of ADHD symptoms, compared to those that were not prenatally exposed and then interventions aided their course.[28]

Stress and Dose Stratification

Another common covariable is stress in pregnancy. Motlagh et al. examines the relationship between ADHD in offspring and maternal smoking as well as maternal stress. Oftentimes, stress and smoking correlate to one another, and many parents who smoke say that they do in response to stress, either from work, homelife, or bodily stress. "Individuals with ADHD alone had the highest rate of heavy maternal smoking during pregnancy (17.3%)".[25] They continued, "the children whose families had only limited ability to cope with psychosocial stressors were more likely to fall in the ADHD category group compared to unaffected control children ($p < 0.0002$)".[25] Considering the reason behind smoking, especially in pregnancy, is crucial to the understanding and stratified risk associated with maternal actions and developing a quit plan or providing personalized patient education with their options is important in prenatal care.

When expecting mothers that previously smoked prior to pregnancy are seeking medical advice and recommendations for plans to quit to decrease their potential risk, non-nicotine options should be considerably exhausted before the use of such methods is implemented. When given things such as NRT, where nicotine is still being administered, the efficacy comes to question. Largely, there is a benefit to go through a smoking cessation process, due to many other toxins in cigarettes, but if these women are still receiving nicotine as part of their program, they should be informed of the potential risks.

A large study in Sweden compared families of siblings and cousins and focused on those that smoked during pregnancy and their development of ADHD. They dose-stratified the study, for those mothers that didn't smoke at all during pregnancy, those that smoked 1-9 cigarettes per day

and those that smoked 10 or more per day.[30] They discovered that those mothers who smoked 10 or more per day had up to a 2.5 times higher risk of developing ADHD than those who didn't smoke, compared to up to a 1.89 times higher risk if they smoked 1-9 cigarettes per day.[30] Interestingly, this may indicate a dose- dependent relationship. In other words, the more a pregnant mother smokes, the risk of the fetus developing ADHD.

Several studies have also presented the correlation between the amount of maternal smoking or nicotine exposure and the severity of the neurodevelopmental disorder. "Compared to the mothers of unaffected control children, the mothers of children with ADHD alone reported higher rates of heavy smoking (>10 cigarettes per day) during pregnancy ($p < 0.01$) and higher levels of severe psychosocial stress during pregnancy ($p<0.002$).[25] Joelsson et al. suggests that "there is a linear correlation between the number of cigarettes smoked during pregnancy and severity of attentional problems. The pathology of this could be caused by chronic hypoxia to the fetus, as some animal models have shown there to be an association between fetal brain hypoxia and ADHD like behavior".[21]

Summary

In summary, collectively, the data suggests a strong correlation between prenatal smoking/nicotine exposure and the development of behavioral disorders, such as ADHD. With the results showing statistical significance in large, more recent studies, suggesting this association. As Tiesler and Heinrich stated in their summative review, "Prenatal nicotine exposure has been associated with altered brain structure and function in human offspring, and a proposed biological mechanism is related to nicotine's adverse influence on neurotransmitter systems during brain development".[5] They continue to state that as the quantity of studies on the topic increases and more sufficient data is able to link the prenatal exposure to nicotine to

behavioral disorders, it is important to recognize that parents should be advised to consider smoking cessation.[5]

Methods

A literature search was conducted using the Lindell Library through Augsburg University and PubMed databases. The search terms used for the purposes of this research were: 'Smoking exposure during pregnancy AND ADHD', as well as 'Nicotine AND Pregnancy AND ADHD'. The publication dates were restricted to include articles from 2011 to 2020, to ensure only the most recent data was used for the purposes of this paper. To note, some studies did reference older studies in their publications in combination with their more recent data. Between the two search terms and parameters set, there were a total of 394 articles. The articles were then sorted by 'peer reviewed' articles only, and information was then used from a total of 22 articles in this review.

Similarly, there were also Google searches conducted to find specific websites for reference for direct-from-the-source information regarding today's recommendations and practices. A few examples of these searches include 'CDC Diagnosis of ADHD', 'American College of Obstetricians and Gynecologists and smoking recommendations', and 'Nicotine Replacement Therapy for Quitting Tobacco'. From these Google searches, several peer-reviewed scientific articles were also used for data purposes. A total of 12 sources found using this method were used in this paper.

For completeness of this review, articles that prove and reject the hypothesis were utilized, and the sources were screened using these criteria. Articles were also screened for content base, to eliminate repetitive information from similar articles. Preference was given to studies that were of large sample size, large summative reviews, and most recent information or data collection.

Preference was also given to data that was statistically significant, using a p-value <0.05 to represent in this paper, however information from non-statistically significant research was also utilized.

In an attempt to represent an inclusive and whole review, articles were also chosen based on location of study, to ensure data was collected worldwide in an attempt to avoid cultural or regional bias, and in various formats. An assortment of prospective, retrospective, observational, interventional, and review articles were applied for variety and extensiveness. This research was completed over the course of two months, between May and June of 2020, and articles first listed during that time frame that fit the aforementioned criteria and preferences using both search sources were selected first.

Discussion

Smoking during pregnancy is a worldwide health issue needing to be addressed, with one fourth of the pregnant population continuing to smoke throughout their pregnancy.[4] With the prevalence of ADHD diagnosis increasing annually, as well as the long term financial and emotional burdens of the diagnosis,[3] understanding the etiology is crucial to preventing the development of the disorder. The purpose of this paper was to determine if nicotine exposure in utero increased the risk of developing ADHD.

Although many studies have concluded the relationship is statistically significant, there are some studies that haven't been able to make the same association. One critique a particular study largely addressed was that there are far too many confounding variables to make certain that there is adequate control with observational designs.[31] They then used a different form of natural experiment, to attempt to separate prenatal environment from inherited effects. It does address an interesting point in that majority of the mothers who continue to smoke during pregnancy, tend

to have a range of maternal characteristics, including maternal genetic factors that may pass on to their offspring. The study consisted of analyzing offspring of women that were conceived through artificial reproduction technologies (ART), attempting to eliminate the genetic factors of maternal smoking and possible genotypic effects biologically.[31] However, in order to have substantiality against some of the aforementioned much larger observational studies. Future studies in this format to represent a larger sample size and quantity of studies are needed, in order to be considered. These methods, as they mention, attempt to address one of the many confounding variables, however there is some critique in their methods. Of those mothers that were selected, if they were going through ART, many of those mothers have already exhausted other options for conception, and are afraid of 'pregnancy failure' and therefore are more likely to take better care of their bodies as they go through pregnancy. Only 6% of their sample continued to smoke during pregnancy, compared to a larger proportion of women in a larger population. There is also the issue of subject selection with studies as such, considering those who are of socioeconomic status that can undergo such therapies, addressing cost, accessibility, and education.

When analyzing and using data as such, it's important to address the subject as a whole, and understand how external factors may significantly affect the study and outcomes. According to Figure 6, from Ellis et al., the lower socioeconomic status, the more likely subjects were to increase cigarettes per day.[27] Likewise, the marital status, and race all seemingly affect or correlate with smoking status and amount. Ball et al. finds similar results. This was a study done in the 1950s and used self-reporting methods. Their results demonstrate that there is no association between SDP and development of ADHD, and state that there should continue to be more research on this topic.[32]

Using this perspective to challenge the hypothesis, few studies that have been unable to make the association, or whose data is undetermined, as well as those that oppose the correlation. A study done using artificial reproductive technologies to eliminate inherited genetic factors and more strictly study the environmental effects concludes that in non-related offspring, maternal smoking was not found to statistically have an effect on ADHD development, whereas it did in related pairs.[31] Their data suggests that ADHD is more of an inherited disorder, rather than explicitly because of environmental toxins in utero, so they took fertilized embryos from non-related pairs and using ART, measured the outcomes based on number of ADHD symptoms found in those babies that were not genetically related, rather only environmentally controlled. Some areas of discussion for this format of study are the age of those that are typically using reproductive technologies, their socioeconomic status, and those willing to continue to smoke, all things considered, for purposes of the study. A study, as such, would be most ideal if it had a significantly increased sample size, and potentially some animal studies to better control confounding variables.

One of the biggest obstacles in this particular research topic is the idea that confounding variables were such a major role in the success of a study, and the validity of the results. The issue with these studies is that there are so many confounding variables that it is difficult to discern the direct correlation between two topics, when years of exposure are in between the use of a substance, like nicotine, and the diagnosis of a disorder, such as ADHD. Between the perinatal period where the exposure would occur, and the age of diagnosis being in mid-childhood, there are so many other factors that influence child development, including environmental exposures, genetic causes, and the changing diagnostic criteria for such disorders, as well as the amount of time being largely limiting, making a study as such difficult to follow

and conduct. A study done by Sciberras et al. mentions an interesting perspective, and states that with the current available studies, there is no way to conclude or confirm that there is a direct causal relationship between PNE and ADHD.[18] They also discuss that there needs to be "a new benchmark for studies investigating the etiology of ADHD whereby there is an expectation not only that data will be collected prospectively but also that the design allows the broad range of genetic and familial factors to be accounted for".[18]

As the Gatzke-Kopp and Beauchaine study discusses above, a limitation in the majority of these utilized studies is that they primarily consider maternal smoking habits, rather than smoke exposure in general.[2] Things such as secondhand smoke exposure and nicotine content in smoking environments. Similarly, paternal patterns of smoking, either providing secondhand smoke to the pregnant mother, or as McCarthy noted, the alterations to the sperm when men smoke and the subsequent effects from those changes.[15] In future studies, utilizing maternal self-reporting measures, as many of these studies used for their data collection, should also include second hand smoke exposures and paternal information to be complete. The complexity of including this information in the research can largely affect the education and recommendations for families during prenatal visits.

This topic is also largely limited to certain formats of studies. There are legal and ethical issues with conducting this study in certain study formats, such as randomized control trials, because it is not ethical to require pregnant women to smoke. There is the idea to utilize those that are smoking while pregnant as the subjects, and randomizing their smoking contents, i.e. having some women get nicotine products and others not. However, the issue with that is if women that are smoking for the fixation, or need for nicotine, and they are not getting it, they may be putting the baby or themselves at more risk due to increased stress or find a different, potentially more

harmful, habit to fulfill their needs. Because of this limitation, this particular topic tends to be more limited to observational studies, and of those, many of them are retrospective, using maternal reporting as a form of data collecting for prenatal exposure. Of those that are prospective, they need such a large sample size, and to be able to follow all the individuals in given various locations over the course of several years. The sample size needs to be considerable, noting the statistic that less than 10% of children will likely be diagnosed with ADHD on average, so the other 90% without ADHD would comprise the majority of the sample size, which further limits the data collection.

Of note, the socioeconomic variables should also be considered when designing subsequent studies. Tzoumakis et al. adds that there are many factors that may be affecting the study to account for.[22] For instance, "mothers who reported heavy smoking during pregnancy also attended their first prenatal visit on average approximately 2 weeks later than non smoking mothers at approximately 15 weeks".[22] They also state that as the quantity of parental smoking increased, so did young maternal age at child's birth, socioeconomic disadvantage, maternal substance use problems, and paternal offending.[22] Ball et al. adds that "women who did not smoke during pregnancy reported more years of maternal education, had lower rates of family psychopathology, and were more likely to report being married compared to those women who smoked at least half a pack of cigarettes per day during pregnancy".[32] With all considered, as further design studies are established, population sample needs to be widely considered if attempting to account for confounding factors that may skew data. Although many of the studies acknowledge their study flaws or areas of areas of discontent, a few others noted were sample size, subject selection, and location biases.

A limitation to note throughout this paper is the change in the common diagnostic tool of

ADHD, the Diagnostic and Statistical Manual of Mental Disorders (DSM) over the last few years. In 2013, the DSM IV changed to the DSM V, and with that change, the criteria for diagnosis of ADHD changed slightly.[33] The changes to note were that there were more examples listed of how ADHD may present in children, adolescents and adults, as well as the criterion list changed from needing six criteria to only needing five to now be diagnosed with ADHD.[33] Using studies that were published prior to or studies that started before the publication date of the new, or current, DSM may present a slight alteration of some of the results. A critique would be to only use publications that were following only one diagnostic tool, or only use studies that were started after 2013 to ensure consistency in the diagnosis of ADHD.

Throughout the research, there were a wide range of variables attempting to be accounted for, study considerations, and some rather inconclusive data regarding the topic. Acknowledgment is given that many of these studies are inconclusive, and that more studies need to be done in various areas. One area of particular interest is continued research in the use of vaping devices, or even those with use of NRT to analyze a direct nicotine exposure, rather than having so many other products and chemicals in tobacco, or other substances. If NRT gives the same amount of nicotine to a person as their tobacco, the use of NRT wouldn't technically be any safer in regard to decreased risk of developing these disorders; however, some forms would be recommended over the use of cigarettes or e-cigarettes because of the other harmful chemicals that are in tobacco products. It is recommended to only refer to the use of NRT in pregnant women when they are unable to quit on their own by their own safe means. If a pregnant woman is to use NRT, the safest option to use is nicotine lozenges, mouth spray, gum, or inhaler, as they tend to have a lower daily dose of nicotine than the patch.[32]

As discovered, the risk of having associated risks for ADHD, i.e. stress and smoking together, or

used to manage the other, validated the initial interest in the topic. When pregnant women that rely on or refer to smoking are under stress, for a variety of reasons, many of them tend to smoke to attempt to relieve that stress. The issue arises when there isn't a safe way to otherwise manage that stress and smoking is their only found relief. If both stress and smoking have an increased incidence for causal ADHD symptoms, managing and eliminating or reducing both would be ideal, but many options for treatment plans include nicotine to some degree, still putting the growing fetus at risk. This puts mothers, and healthcare providers, in a situation to play a "which is worse" scenario. Is it better for the mother to be under considerable stress, which can be hard on her and the baby, as well as have these studied consequences, or allow her to indulge in smoking a few cigarettes to reduce the stress, and expose the mother and baby to smoke and nicotine? Based on this research, is it indicated that no amount of nicotine while pregnant is safe, but there is a significant increased risk with higher doses of nicotine, so tailoring nicotine intake, if needed, for mothers that are struggling is likely the best way to manage it, while attempting to minimize the risk of the fetus for discussed sequelae.

Conclusion

For many reasons, smoking or nicotine exposure while pregnant or in the perinatal period is not recommended, but for the purposes of this study, due to the risk of associated disorders, pregnant women should be informed about the potential risks associated with their exposures. Even though some older studies, mentioned throughout, have suggested that ADHD is inherited rather than environmentally influenced in etiology, the endless studies that suggest otherwise are generally convincing with quality research supporting the evidence. The difficulty comes when trying to assist with smoking cessation while pregnant. Ideally, no nicotine therapy would be needed; however, understanding that is not always possible, it is important to fully disclose the

possible risks of nicotine exposure to the fetus. Although there are some studies that question whether it is actually a causation, there is substantial evidence and studies that support the hypothesis indicating there is a relationship between the two.

In general, there needs to be continued research on the topic using a variety of methods and populations, with various sources of nicotine. Before making it an official recommendation to forego all nicotine containing products while pregnant, including the use of NRT as a method of quitting, substantial research needs to be completed. This would need to compare those that use NRT to those that do not, in previously smoking mothers. This, understandably, presents several ethical issues, unless specific guidelines in methods are in place. Smoking while pregnant should continue to be recommended against, but the efficacy and causation needs to be clarified and further studied with other nicotine containing products.

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Appendix

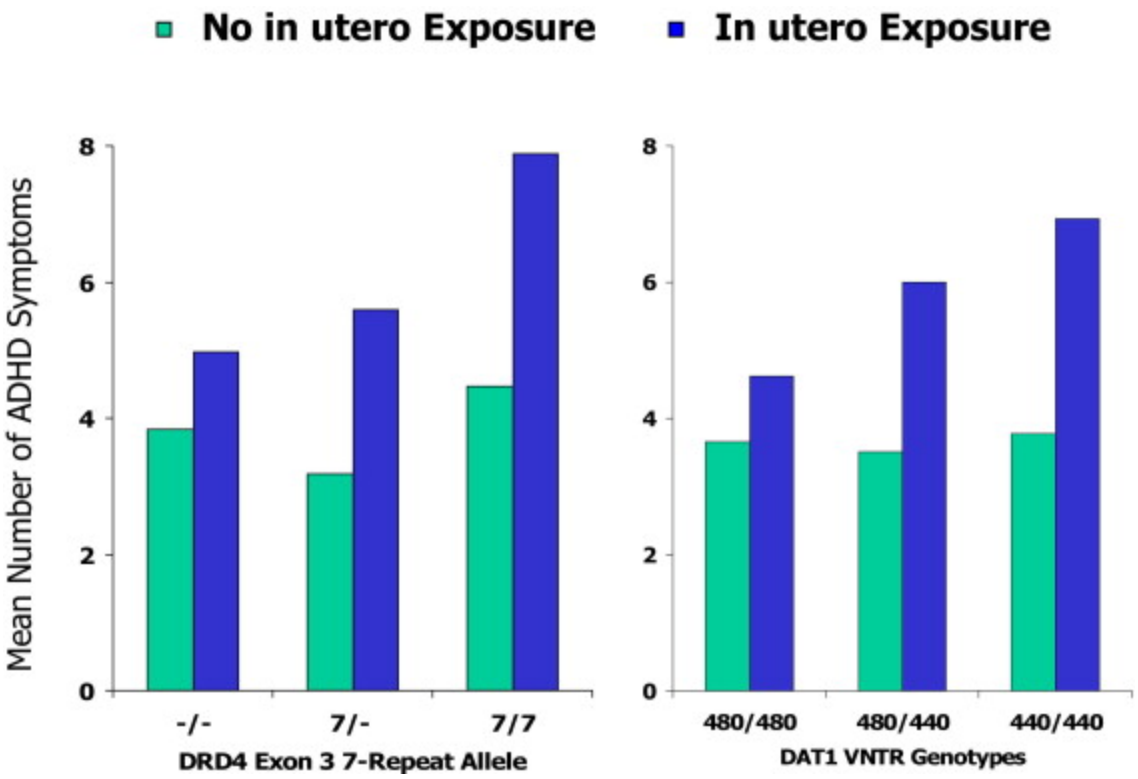

Figure 1[20]: demonstrating the difference between smoke exposure and the control, without smoke exposure in utero, and the two different genotypes studied, showing an increased number of at risk alleles in those exposed.

Table 3 Odds ratio (OR estimate, CI and *p* values) psychiatric disorders, for children exposed to smoking any time during pregnancy

	Disorder		
	ADHD ($n = 34$)	ODD ($n = 57$)	ADHD and ODD ($n = 13$)
Unadjusted	3.25 (2.08–5.09), $p < 0.001$	3.12 (2.30–4.24), $p < 0.001$	3.67 (1.82–7.40), $p < 0.001$
Adjusted for propensity score stratified in quintiles	2.59 (1.50–4.34), $p < 0.001$	2.69 (1.84–3.91), $p < 0.001$	3.69 (1.68–8.14), $p < 0.001$
Adjusted for propensity score as covariate	2.17 (1.30–3.61), $p = 0.003$	2.46 (1.66–3.63), $p < 0.001$	2.68 (1.84–3.91), $p < 0.001$

Figure 2: Ellis et al.'s results showing the odds ratio while accounting for maternal confounding variables and measuring for both ADHD, as well as ODD (oppositional defiant disorder).[27]

Table 4 Associations between ADHD and maternal smoking during pregnancy among comorbid neuropsychiatric conditions

	Cases exposed to smoking during pregnancy *n* (%)	Controls exposed to smoking during pregnancy *n* (%)	OR (95 % CI) Unadjusted	OR (95 % CI) Adjusted[a]
ADHD + Mental Retardation (*N* = 374)	106 (28.3 %)	173 (12.6 %)	2.79 (2.10–3.72)	1.93 (1.38–2.69)
ADHD + ASD (*n* = 1134)	299 (26.4 %)	593 (14.3 %)	2.14 (1.82–2.51)	1.59 (1.33–1.91)
ADHD + Tourette (*n* = 172)	45 (26.2 %)	89 (14.3 %)	2.06 (1.36–3.13)	1.74 (1.06–2.86)
ADHD + CD/ODD (*n* = 2339)	950 (40.6 %)	1308 (15.4 %)	3.96 (3.55–4.41)	2.54 (2.24–2.88)[b]
ADHD + Learning and coordination disorders (*n* = 2957)	799 (27.0 %)	1726 (16.0 %)	1.98 (1.80–2.19)	1.51 (1.35–1.68)
ADHD without comorbidities (*n* = 3136)	865 (27.6 %)	1764 (15.4 %)	2.11 (1.92–2.32)	1.59 (1.43–1.77)

Reference category in each group were their designated controls
OR odds ratio, *CI* confidence interval
[a]Adjusted for:maternal and paternal psychiatric history, maternal substance abuse history, maternal and paternal age at birth, maternal socioeconomic status, birth weight for gestational age, number of previous births and maternal marital status
[b]OR was significantly different from "ADHD without comorbidities", $p < 0.001$

Figure 3[21]: relationship between ADHD and maternal smoking during pregnancy along with comorbid conditions.

Table 2 Simultaneous multiple regression analysis evaluating smoke exposure as a predictor of conduct disorder and ADHD symptoms

Variable	B	SE B	β	*P*
Conduct disorder				
Income	−0.02	0.02	−.14	.181
Maternal ASPD	0.16	0.18	.08	.377
Paternal ASPD	0.18	0.22	.08	.423
Birth weight	0.30	0.45	.07	.502
Gestational age	0.05	0.23	.02	.839
Substance use	−2.07	2.11	−.09	.328
Smoke exposure	0.44	0.17	.24*	.013
ADHD				
Income	−0.04	0.034	−.13	.194
Maternal ASPD	0.24	0.363	.06	.517
Paternal ASPD	0.17	0.456	.04	.709
Birth weight	−1.15	0.92	−.14	.215
Gestational age	.57	0.49	.13	.240
Substance use	−2.67	4.35	−.06	.540
Smoke exposure	.98	.36	.25	.007

Note. $N = 117$
*$P < .05$

Figure 5: Gatzke-Kopp and Beauchaine's table analyzing the common confounding familial factors, highlighting that smoke exposure was the only statistically significant coefficient.[2]

Demographic characteristics stratified by maternal prenatal smoking.

	Maternal smoking during pregnancy			
	None	<Half pack per day	Half to full pack per day	>1 Pack per day
	N = 812	*N* = 482	*N* = 515	*N* = 215
Offspring characteristics				
Age, years	37.4 ± 3.4	37.1 ± 3.3	37.3 ± 3.2	37.1 ± 3.3
Male	46.6 (378)	46.7 (225)	43.5 (224)	48.8 (105)
Race, White	83.7 (673)	80.2 (381)	89.2 (452)	95.8 (206)
Family psychopathology[a]	8 (65)	11 (53)	12 (62)	17 (37)
Low birthweight, <2500 g	5.0 (41)	7.6 (37)	8.5 (44)	17.7 (38)
Maternal characteristics				
SES, low	41.9 (328)	48.8 (230)	52.5 (260)	51.5 (105)
Education, years	11.7 ± 3.4	11.4 ± 3.4	10.9 ± .0	10.6 ± 2.6
Marital status	90.2 (716)	83.7 (399)	86.5 (434)	82.2 (171)
Study enrollment				
First trimester	37.7 (306)	31.3 (151)	30.7 (158)	36.7 (79)
Second trimester	49.8 (404)	50.6 (244)	51.8 (267)	47.0 (101)
Third trimester	12.6 (102)	18.1 (87)	17.5 (90)	16.3 (35)
# of prenatal visits	9.0 ± 3.6	8.8 ± 3.8	8.5 ± 3.7	8.3 ± 4.0
Ascertainment source, NEFS	66.8 (542)	61.6 (297)	64.9 (334)	65.6 (141)

Numbers in table presented as percent (*N*) or mean ± standard deviation.
[a] Includes report of psychopathology in subjects' parents, grandparents, aunts or uncles.

Figure 6: Demographics demonstrated by maternal prenatal smoking.[27]

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