Impact of prenatal risk factors in attention deficit hyperactivity disorders: potential for gene–environment interactions

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Abstract
Attention deficit hyperactivity disorder (ADHD) is a multifactorial disorder and both genetic and environmental factors have been implicated in its etiology. Yet, the interaction between genes and environment is seldom studied directly. This article considers the plausibility of nicotine exposure during prenatal development as well as postnatal factors in the etiology of ADHD. The few existing studies show inconsistent results, but provide preliminary evidence suggesting that nicotine exposure together with genes in the dopaminergic system confer risk for ADHD. Factors affecting resilience during prenatal and postnatal development remain virtually unexplored. Recommendations for future research are provided.

Keywords ADHD; environmental; etiology; gene–environment interaction; genetic; maternal smoking; methodological issues; postnatal; prenatal; resilience

Traditionally, genetic contribution to traits was viewed as deterministic. The realization that the aetiology of complex traits depends on contributions from both genes and the environment \(^1\,^2\) enables an understanding of causal pathways that lead to psychiatric disorders and opens a window of possibility for prevention. Attention deficit hyperactivity disorder (ADHD) has a strong genetic component, most likely consisting of multiple genes, with each having a small effect size. \(^3\) Understanding the gene–environment interaction for the aetiology of ADHD is an enormous, yet exciting, task that has potential for future innovative diagnostic and treatment options as well as for prevention. This brief overview highlights possible gene–environment interactions from a life-course perspective, with a special focus on prenatal development and smoking exposure.

Genes are linked to psychiatric endpoints via a series of intermediate, endophenotypic steps spanning from protein coding to neural system dysfunctions to symptoms. \(^4\) Environmental forces are likely to exert an influence at each step along the causal pathway and potentially lead to alterations in the developmental trajectory. There are many possibilities for environmental interplay as brain development entails both progressive (e.g. increase in synaptic density, myelination) and regressive (e.g. pruning) actions to achieve efficiency. \(^5\) The most dramatic and rapid period of brain development in the lifespan occurs prenatally. Although brain growth is driven genetically, environmental signals are detected by the developing embryo that lead to a host of adaptations, including epigenetic programming, that can have long-term consequences. \(^6\) Because prenatal insults can affect future, yet undeveloped, cells. \(^7\) Several environmental factors related to maternal lifestyle during pregnancy have been proposed, and smoking has received considerable research attention. \(^8\)

Animal models of prenatal nicotine exposure
Experimental work demonstrates that nicotine exposure during prenatal brain development evokes permanent changes in synaptic function, altering patterns of neural cell replication, differentiation, and synaptogenesis. \(^9\,^10\) A key element is that stimulation of the nicotinic cholinergic receptors is ultimately linked to reduced DNA content in the hippocampus, a significant region for cognition, learning, and memory. \(^7\) Initial structural changes in the hippocampus alter the programmed chain of events of normal brain development, even affecting cells that emerge later during postnatal life. \(^7\) Cell signalling involving the dopaminergic and serotonergic neurotransmitter systems is disrupted in response to nicotine exposure. \(^11\) These neurotransmitters act as neural morphogens during frontal cortical formation and differentiation, and these early disturbances may be reflected in neuro-anatomical differences later in the lifespan. \(^12\)

Thus, biological mechanisms can plausibly link nicotine exposure with adverse fetal brain alterations that can impact upon behavioural and cognitive outcomes related to ADHD. Yet translation of results from animal models to humans is not without difficulty; for example, prenatal brain development is prolonged in humans, raising the issue of critical periods of exposure.

Studies of prenatal maternal smoking
Prospective epidemiological studies have shown that smoking during pregnancy increases the likelihood of ADHD or ADHD symptoms in children. \(^9\,^13\,^14\) However, an important issue in human studies is the added complexity resulting from selection bias. Smoking may be used as a way to alleviate ADHD-like symptoms, \(^16\) and a few retrospective studies have shown that smoking is more common among adolescents and young adults with ADHD. \(^17\,^18\) Nicotine dependency is also more severe among persons with ADHD than controls. \(^18\) A retrospective twin study of male-only pairs revealed a substantial genetic contribution to smoking, although the relative degree of genetic impact varied across ages from adolescence to 35 years. \(^19\) Thus, a genetic predisposition in mothers may increase the risk of smoking during pregnancy and present a source of residual confounding, which makes it difficult to distinguish the relative causality linked to genes and smoking exposure.

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Two large-scale epidemiological studies have attempted to address this issue. Researchers within the Nordic Network on ADHD compared populations varying in prevalence rates of smoking, reasoning that in a society where smoking was uncommon, continued smoking in pregnancy could reflect genetic loading. Results supported the direct link between smoking exposure and ADHD symptoms. In another study, the entire Finnish population of children born between 1987 and 2001, consisting of 892,796 subjects, is being examined. Data are derived from linkage between two national population registries: the Finnish Medical Birth Register, which includes information on routine medical and social data from prenatal, perinatal, and postpartum periods, and the Hospital Discharge Register, which covers all in-patient and out-patient visits in Finland and includes diagnoses. The analytical strategy is to estimate the risk of diagnosed ADHD in children exposed to maternal smoking in utero in comparison with the risk in those unexposed in the whole population while controlling for sociodemographic factors and birth outcomes. Furthermore, the sample size has permitted a nested matched-sibling design examining all same-sex siblings who are discordant with regard to maternal smoking. This study will be able to provide important insight at the population level into the causality of smoking exposure for ADHD in children. If the associations hold after control for family factors, then a causal association will be supported.

The placenta is critical for intrauterine development through its transport of oxygen, nutrients, and endocrine function. At the interface between the maternal–fetal compartments, the placenta is highly responsive to environmental cues, making the adaptations that are necessary to maximize viability and fetal growth. The placenta is able to filter many toxins, but not nicotine and cotinine, which pass freely across to the fetus. Nicotine exposure can be observed as placental morphological damage and reduction in the ability to perform all biological functions; therefore, it is likely that environmental and genetic factors could affect fetal brain development by way of the placenta. This possible mechanism has received little research attention.

**Gene–environment interactions**

**During prenatal development**

To date, only a handful of studies have examined GxE using genetic analysis, focusing primarily on dopamine genes as these have been most widely associated with ADHD. Kahn and colleagues used a retrospective design to assess prenatal smoking exposure on a yes/no basis. They found a significant interaction, showing that DAT polymorphism was associated with parental ratings of child hyperactivity only when children had been exposed to maternal prenatal smoking. Other clinical studies, however, also using retrospective maternal report of smoking in pregnancy, found no evidence for GxE with respect to dopamine (DRD4, DRD5, and DAT1) and serotonin (5HTT) genes. Neuman and co-workers used a large sample of twins and found that DRD4 and DAT1 genes interacted with maternal prenatal smoking, resulting in an increased risk for the severe form of ADHD combined subtype (i.e. fulfilling the criteria for both inattention and hyperactivity–impulsivity). Becker et al found that risk for current and lifetime hyperactivity–impulsivity was significantly increased among boys with DAT1 (+/+) who had been exposed to maternal smoking in utero. Other subtypes were not affected, nor were girls.

These studies provide important aetiological clues and call for further research that addresses sampling issues and includes information regarding parental psychopathology. Epigenetic processes (those related to gene expression) are under environmental influence and may account for the observed discrepancies in genetic studies. A better understanding of how epigenetic regulation contributes to the aetiology, developmental course, and severity of ADHD will provide novel insights into prevention and treatment options.

Because experimental evidence exists and plausible biological pathways have been sketched (although they are far from being fully delineated), it is likely that prenatal exposure to nicotine will be found to play a causal role in the aetiology of ADHD – albeit possibly conditional on genetic liability and/or other environmental insults. Just as the genetic contribution doubtless comprises a number of genes, so too is the environmental contribution likely to consist of a number factors, each adding to the outcome. Multiple environmental factors not only make the task of deciphering causality and implementing interventions challenging, but they also create options for multiple ways of intervening to ameliorate environmental insults. One such factor is maternal stress during pregnancy, as this has been linked to ADHD symptoms in children and also to smoking and other negative behaviours and emotional states.

**In relation to postnatal environment**

The intrauterine environment is likely to play a key role in the aetiology of psychopathology due to the rapid brain development that takes place prenatally. Nonetheless, the impact of prenatal risk factors in ADHD should be considered in the light of postnatal environmental conditions, because neurodevelopmental processes continue into young adulthood. The adolescent brain is susceptible to the neurotoxic effect of nicotine in much the same way as the fetal brain, although to a lesser extent. Prenatal nicotine exposure is likely to increase risk of adolescent smoking and ultimately reinforce cognitive deficits due to the double exposure.

Postnatal environments characterized by social adversity, despite variations in definition, have repeatedly been found to contribute to ADHD symptoms in diverse samples of children. Social programming, perhaps via stressful life circumstances, may well accentuate symptoms or trigger underlying dispositional early stress potentially leads to enduring changes in brain development via alterations of, for example, the hypothalamic–pituitary–adrenal (HPA) axis. For example, Romanian children institutionalized early in life have shown signs of neurobehavioral impairment reminiscent of ADHD-like symptoms. Environmental mediation of risk could be viewed as bi-directional, whereby the opposite possibility, that environmental factors may confer protection, may also be true.

**Gene–environment interactions and resilience**

The notion of resilience refers to factors, whether they be environmental or genetic, that buffer against poor outcomes in the face of adverse conditions. Few studies have considered
resilience in relation to ADHD. Resiliency factors may operate during pregnancy. Ideally, pregnancy should be related to psychological well-being and positive anticipation of a new family member. Positive adaptation to pregnancy has been associated with heightened health awareness and reduced smoking.20 Moreover, feelings of happiness correlate with relevant biological processes including neuro-endocrine function,39 which is a hypothesized mechanism affecting prenatal brain development.40 However, the research emphasis is overwhelmingly on risk factors such as stress, rather than well-being. It may be that research attention directed towards salutary factors may lead to the identification of strategies that clinicians working with pregnant women in the future might implement to counteract genetic and environmental risk factors.

Postnatal environmental factors may allow for the reversal or rebound of previous prenatal insults. Rats exposed to ‘nurturing’ maternal behaviours such as licking and grooming are less fearful and have attenuated stress responses.41 Further work by Meany’s group showed that these behavioural and neuro-endocrine outcomes were mediated via epigenetic mechanisms,42 although much work is still necessary to determine how maternal care is transformed into a wide variety of behavioural outcomes, and whether these apply to humans.43

Genetic factors are also likely to play an important role in protecting from adverse environments. Nigg and colleagues14 selected dopaminergic and noradrenergic genes because previous research had shown their expression in the prefrontal cortex and relation to ADHD. Genetic markers were pooled to examine the composite risk and the results showed that children whose genotypes exemplified lower risk were less likely to meet the ADHD diagnostic criteria and were thus resilient, despite exposure to an adverse environment.34

Future research

Research methods need to be improved so that estimates can be more precise. To this end, it is essential that scientists use prospective measures that are obtained as objectively as possible, in order to disentangle residual confounding due to reporting bias. Less explored plausible mechanisms, such as placental function, should be studied. Data should be collected on parental psychopathology, as this variable is relevant for both genetic and environmental forces – for example in relation to potentially negative parenting. Use of large-scale community samples would enable stratification by key exposures and the detection of dose–response relations. Longitudinal studies can identify time windows during which the effects of exposures are greatest in humans. Developmental effects can also be identified in longitudinal design. Because the relative contribution of genes and environment can differ across ages,19 studies need to be powered sufficiently to detect possible differences within narrow age bands. Longitudinal analysis of brain morphology shows that distinct patterns of development are associated with worsening of symptoms and with clinical improvement.44 Multidisciplinary teams, using combined genetic and lifespan approaches, need to join forces in order to be able to coordinate various levels of analysis, including molecular, neuropsychological and phenotypic. In this way, differences that correspond to gene and environmental exposures can be identified.

Conclusion

Determining causality is difficult owing to the multifactorial nature of ADHD. The pathway linking genes to psychiatric outcomes is long and intricate, making detection of causal factors especially challenging. There is potential for genetic–environmental interplay at every step of the way. With regard to nicotine exposure for ADHD risk, it seems likely that the relationship will be causal to some degree, at least for some people. As gene–gene interactions are possible, so too environment–environment interactions may be likely. Multiple environmental exposures may be particularly important in social programming, because negative environments can perpetuate or exacerbate symptoms. However, true causal associations may be obscured by resiliency factors if they are able to counteract some previous damage. This scenario is frustrating for the scientist in search of causal factors, but rewarding for clinicians working to ameliorate ADHD-related distress.

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