FACING ADHD TOGETHER

Understanding Environmental Exposures and ADHD: A Pathway Forward

Stephen V. Faraone

Identifying a common, modifiable environmental cause for attention deficit/ hyperactivity disorder (ADHD) would guide the development of preventive interventions to improve outcomes. Whereas many environmental risk factors have been documented for ADHD, common causes have yet to be identified. In a comprehensive and fascinating overview about the current state of research on gene-environment correlations and polygenic risk scores, Professor Stephen Faraone provided a glimpse into the puzzle of how genetics and environment are interacting.

KEY STATEMENTS

In order to move forward in studying environmental risk factors

- Use genetically informative designs
- Address all potential confounds including those that are not measured
- Study and adjust for the entire exposome
- Do not rely on rodent exposure models
- Conduct clinically useful studies of course modifiers
- Avoid therapeutic nihilism (just because the causes might be primarily genetic does not mean that psychological behavioural therapies are not useful)

Genetic and Environmental Causes of ADHD

"Familial and genetic confounding is the most important type of confounding and should be addressed in a genetically informed study."

According to genetic twin studies, about 74 % of ADHD cases in the population can be attributed to the genetic inheritance from our parents. Accordingly, 26 % of cases are caused by environmental factors.[1] Some rare environmental risks have been identified as likely causes of ADHD, such as traumatic brain injury[2] or extreme environmental deprivation.[3] In the past, meta-analyses have been applied to find environmental risk factors of ADHD. However, a common flaw of the observational epidemiologic studies included in these meta-analyses is that the constituent studies could not correct for all possible confounds. The most important type of confounding is familial and genetic confounding. It occurs when the environmental exposure being studied is correlated with either the genetic risk of the disorder being studied or other familial risk factors. For this reason, meta-analyses may have documented confounded associations, which calls for cautious interpretations. Professor Faraone emphasised that addressing familial/genetic confounding requires a genetically informed study.[4]

Gene-Environment Correlation is a Confounding Factor

"Previously considered potential causes for ADHD are merely associations that were observed due to the confounding of genetics."

Professor Faraone described four different types of gene-environment correlations. The passive type occurs when parents provide both, genes and environments to their children. The evocative type implies that an individual's genetic traits evoke specific responses from the environment. In the active type individuals actively seek out environments that complement their genetic predispositions, e.g., sensation seeking. In the genetic nurture type, the DNA variant affects parental behaviour in a manner that impacts disease expression in the child.

Gene-environment correlation is very relevant to the environment because it creates confounding. As an example, Professor Faraone cited sibling-control studies, which were applied to several environmental exposures that population studies had implicated in ADHD, for instance maternal obesity, maternal smoking, C-section, oxytocin-induced labour induction, and paracetamol use in pregnancy. When adjusted for genetic confounding, many associations documented by meta-analyses at the population level were no longer statistically significant (Table 1). Thus, the initial thought that these were actually potential causes for ADHD was misleading. Instead, they display merely associations that were observed due to the confounding of genetics.[4]

The Role of Polygenic Risk Scores

"Due to familial confounding, suspected environmental factors are often falsely associated with neurodevelopmental disorders."

Polygenic risk scores (PRS) are widely used to characterise genetic liability for heritable mental disorders, including ADHD. In consequence, polygenetic risk analyses are creating many types of associations that are gene-environment correlations. An increasing body of literature indicates that certain risks previously considered as environmental risks may be the result of genetic confounding. Professor Faraone pointed out that studies on suspected environmental factors often suffer from familial confounding bias when exposures are themselves heritable. This harbours the risk of them being falsely associated with neurodevelopmental disorders, which may result in a wasting of public resources, unnecessary worry, misleading advice, and eroded public trust.[5]

Professor Faraone presented various examples of gene-environment correlations, in which the PRS for ADHD was associated with perceived stress,[6] exposure to adversity,[7] and higher levels of household chaos.[8] A study examining gene-environment correlation for parenting dimensions suggested that youth PRS significantly predicted higher levels of youth ADHD symptoms. That, in turn, predicted lower levels of parental involvement, higher levels of poor supervision/monitoring, and higher levels of inconsistent discipline. Due to the evocative type of environment, the child's behaviour is affecting parents' response to them.[9] A study distinguishing between transmitted and non-transmitted alleles in genetic transmission from parent to offspring demonstrated that the associations between parent characteristics and offspring outcomes in childhood are mainly attributable to the effects of genes that are shared by parents and children.[10]

Gene-Environment Interaction in ADHD

Gene-environment interaction means that the effect of a gene depends upon the person's environment, or that the effect of an environmental risk depends upon the person's genetic makeup. Yet, the majority of conducted studies did not reveal any interaction with polygenic risk scores. Can animal models solve the environment-risk dilemma? Professor Faraone summarised the limits of animal studies on ADHD. As a behaviourally defined disorder of unknown aetiology and pathophysiology, ADHD presents specific challenges for the development of animal models. ADHD symptoms are present to some degree also in the normal population, posing the difficulty of what to consider abnormal in the animal model and what to use as a control.

Parallels Between Genomic & Exposure Research

"An exposome-wide approach is the only way to move forward in exposure epidemiology."

In its early stages, genetic research tested the association of psychiatric disorders with candidate genes. Likewise, researchers have focused on candidate exposures. After complete failure of the candidate gene approach in psychiatric genetics, progress with a genome-wide approach created solid results. In parallel, an exposome is a comprehensive collection of environmental factors that the foetus of a pregnant woman is exposed to from conception to birth. Professor Faraone considers an "exposome-wide" approach as the only way to move forward in exposure epidemiology.

Since confounding causes ambiguity, should we abandon all hope?

"Avoid therapeutic nihilism."

Some exposures should be reduced, regardless of their impact on ADHD (e.g., child abuse, parental psychopathology, family conflict, injuries). More evidence is required for eliminating other risk factors with the specific goal of reducing the risk for ADHD. Despite confounding, the fact that an exposure predicts an outcome, e.g. maternal smoking, if generalisable, may be useful in predicting who is at high risk for ADHD and who is not. However, it may be more useful to study environmental features that worsen or improve symptoms of ADHD. It is important for clinicians to understand that, despite the fact that we lack a good handle on the environmental features causing ADHD, psychological therapies are still useful to help people with ADHD.

		Risk Ratios	
Study	**Risk Factor**	**Main Analysis**	**Sibling Control Analysis**
Chen 2014[11]	Maternal Obesity	aHR=1.64, 95% CI=1.57-1.73	aHR=1.15, 95% CI=0.85-1.56
Skoglund 2014[12]	Maternal smoking (>10 cig/day)	aRR=2.04, 95% CI=1.95-2.13	aRR=0.84, 95% CI=0.65-1.06
Curran 2016[13]	C-section	aHR=1.15, 95% CI=1.11-1.20	aHR=1.05, 95% CI=0.93-1.18
Wiggs 2017[14]	Oxytocin-induced labor induction	aHR=1.23, 95% CI=1.19-1.28	aHR=0.99, 95% CI=0.91-1.07
Axelsson 2019[15]	C-section (intrapartum and prelabor)	aHRIP=1.10, 95% CI=1.04-1.16	aHRIP=1.09, 95% CI=0.97-1.24
Lemelin 2021[16]	Use of ADHD medication	aHR=1.96, 95% CI=1.22-3.15	aHR=1.14, 95% CI=0.62-1.98
Hegvik 2023[17]	Labor epidural analgesia (pooled)	aHR=1.20, 95% CI=1.19-1.21	aHR=0.99, 95% CI=0.96-1.02
Ahlqvist 2024[18]	Acetaminophen (paracetamol) use in pregnancy	aHR=1.07, 95% CI=1.05-1.10	aHR=0.98, 95% CI=0.94-1.02

Table 1: Many risk factors implicated by population studies were refuted by sibling control analyses. Statistical significance is indicated when the confidence interval does not include 1.

aHR: adjusted hazard ratio; aRR: adjusted relative risk; CI: confidence interval; IP: intrapartum

Q&A

During the presentation audience members had the opportunity to ask questions via the chat function.

Is alcohol and drugs or drug use during pregnancy an environmental factor?

Stephen V. Faraone: It would be considered an environmental factor. The alcohol or drug passes through the placenta and affects the foetus in a way that can cause the foetal alcohol syndrome. People have hypothesised it might be associated with ADHD. There are studies that suggest that paternal drinking during pregnancy is associated with ADHD in their children. But we also know that paternal drinking is associated with paternal ADHD. Thus, we have a clear, genetic confound. This has not yet been addressed in a genetically informative design.

Is there a correlation between criminality and ADHD?

Stephen V. Faraone: Absolutely. A meta-analysis investigated the prevalence of ADHD in prison populations. The prevalence of ADHD in adults is around 3 % worldwide, however in prison populations, the average prevalence is around 25 %. A study from Sweden compared periods when patients were on ADHD medication with periods when they were off medication.[19] They connected these time periods with data about criminality in the population registers. Adults with ADHD were more likely to commit crimes when they were not taking their medication compared to times when they were taking their medication.

Could there be several types of ADHD, an ADHD arising from genetic factors alone and an ADHD caused by environmental factors, and a hybrid caused by an interaction between genes and environments?

Stephen V. Faraone: There are some rare environmental risks, such as traumatic brain injury and extreme deprivation. Although there haven't been studies of their polygenic risk, it seems from the magnitude of the odds ratios that we're seeing, that these are real environmental causes.

Are there any genetic links between ADHD and schizophrenia?

Stephen V. Faraone: There is a small genetic link between schizophrenia and ADHD. We know this from the Swedish family studies, which showed a weak association between one family member having schizophrenia and the other having ADHD.[20] There is a small overlap in the genetics, but it's smaller than the overlap, with depression or conduct disorder or autism.

For children with enlarged adenoid and tonsils, we understand that those with ADHD behaviours have been shown to dramatically improve after surgery indicating a close link between obstructive sleep apnoea and ADHD in these children. Are there any data on how relevant this is?

Stephen V. Faraone: A meta-analysis showed that sleep apnoea has been associated with ADHD.[21] Children receiving tonsillectomies show an improvement in the radiation symptoms. The effect size is comparable to that of a non-stimulant medication. Sleep issues are something that clinicians need to assess, particularly sleep apnoea in patients with ADHD.

ABOUT THE EXPERT

Stephen V. Faraone, Ph.D. is a distinguished professor in the Departments of Psychiatry and Neuroscience & Physiology and Director of Research for the Department of Psychiatry at SUNY Upstate Medical University, Syracuse, NY. He is also senior scientific advisor to the research programme in pediatric psychopharmacology at the Massachusetts General Hospital and a lecturer at Harvard Medical School. Professor Faraone is a recipient of numerous awards, including the Lifetime Achievement Award from the International Society of Psychiatric Genetics. He is President of the ADHD World Federation.

References

1. araone SV and Larsson H (2019). Mol Psychiatry 24:562-575.
2. Asarnow RF, et al. (2021). JAMA Pediatr 175:1009-1016.
3. Kennedy M, et al. (2016). J Child Psychol Psychiatry 57:1113-1125.
4. Faraone SV, et al. (2024). Nat Rev Dis Primers 10:11.
5. Carlsson T, et al. (2021). Dev Psychopathol 33:1448-1495.
6. Li JJ (2021). Psychol Med 51:102-111.
7. Zwicker A, et al. (2020). J Child Psychol Psychiatry 61:536-544.
8. Agnew-Blais JC, et al. (2022). J Child Psychol Psychiatry 63:1153-1163.
9. de la Paz L, et al. (2023). Res Child Adolesc Psychopathol 51:665-677.
10. de Zeeuw EL, et al. (2020). Behav Genet 50:221-232.
11. Chen Q, et al. (2014). Int J Epidemiol 43:83-90.
12. Skoglund C, et al. (2014). J Child Psychol Psychiatry 55:61-68.
13. Curran EA, et al. (2016). Int J Epidemiol 45:532-542.
14. Wiggs KK, et al. (2017). Behav Genet 47:383-393.
15. Axelsson PB, et al. (2019). J Child Psychol Psychiatry 60:151-159.
16. Lemelin M, et al. (2021). Eur Neuropsychopharmacol 44:66-78.
17. Hegvik TA, et al. (2023). Am J Obstet Gynecol 228:233.e231-233.e212.
18. Ahlqvist VH, et al. (2024). Jama 331:1205-1214.
19. Lichtenstein P, et al. (2012). N Engl J Med 367:2006-2014.
20. Larsson H, et al. (2013). Br J Psychiatry 203:103-106.
21. Sedky K, et al. (2014). Sleep Med Rev 18:349-356.

EXPERT ADVICE AND RESOURCES

- **Visit www.ADHDevidence.org for:**
  - The International Consensus Statement on ADHD
  - 370 slides from the Consensus Statement for educating others about ADHD
  - Curated evidence about ADHD from new publications

This online seminar was sponsored by

MEDICE
THE HEALTH FAMILY

MEDICE
Arzneimittel Pütter GmbH & Co. KG
Kuhloweg 37
58638 Iserlohn, Germany