

The Causing Factors of Attention-Deficit Hyperactivity Disorder and Its Association with Other Psychiatric and Physical Disorders

Shuhao Li^{1, a, *, †}, Ding Wang^{2, b, *, †}, Yingjie Zhu^{3, c, *, †}

¹School of Arts and Sciences Rutgers University--New Brunswick New Brunswick, United States

²Faculty of Art and Science University of Toronto Toronto, Canada

³Henan Experimental High School Zhengzhou, China

*Corresponding author: ^akevinlsh163@gmail.com, ^brean.wang@mail.utoronto.ca, ^c3232680350@qq.com

[†]These authors contributed equally.

Keywords: Attention-deficit-hyperactivity disorder; Etiology; Family Study; Twin Study; Comorbid disorder

Abstract: Attention-deficit hyperactivity disorder (ADHD) is a major neurodevelopmental health concern characterized by impairing patterns of inattention, impulsivity, and hyperactivity. As the causes of ADHD are multifaceted, this paper explores the etiology of ADHD and its induced factors through assessments of familial aggression and environmental impacts. Family studies and twin studies are involved in explaining the findings. Besides, this paper also aims to evaluate the co-occurrence risk of ADHD with other psychiatric disorders and physical disorders by noticing that comorbidity among this tripartite relationship is significant. Psychiatric comorbidities in ADHD are discussed in terms of mood disorders and substance use disorders; on the other hand, physical diseases mainly cover chronic inflammatory diseases and allergic diseases. Based on the evidence, ADHD is a genetic-related disorder with few shared environmental influences, which means that familial risk increases with a decreasing distance of biological relationships. Also, ADHD has high comorbidities with psychiatric disorders, including bipolar disorder, major depression, anxiety, and substance use disorder. Regarding physical diseases, cystic fibrosis, asthma, allergic rhinitis, and atopic dermatitis are found to coexist with ADHD. From clinical perspectives, our work on familial risk evaluation could facilitate the identification of ADHD in the family units to initiate medical care in the early stage. The co-occurrence feature may provide a detailed overview for exploring more possibilities to establish a more precise and complete diagnostic system.

1. Introduction

Before the contemporary descriptions of attention deficit hyperactivity disorder were integrated into DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) symptoms of inattention, excessive motor activity and impulsiveness were documented by several authors over the past 200 years [1]. For instance, Melchior Adam Weikard, a German physician, in 1775, firstly described attention deficit [2]. In the book entitled *Der philosophische Arzt*, Weikard provides a detailed illustration of the phenomenon that sensory stimuli are capable of drawing the patient's attention and disturbing the patient's thoughts, which occurs most frequently with hearing and sight [2]. Although the clinical characterizations, underlying principles, and terminologies used nowadays largely differ from those adopted in the last 200 years, consistency is found between historical descriptions and modern diagnostic criteria [1]. As described in DSM-5, attention deficit hyperactivity disorder is a type of neurodevelopmental disorder, characterized by impairing levels of inattention and hyperactivity that are developmentally inappropriate for the patient's age. The DSM criteria for attention-deficit hyperactivity disorder (ADHD) is divided into two subcategories---inattention and hyperactivity-impulsivity. To be diagnosed with inattention, the patient should exhibit an inability to stay on task, to be organized or to concentrate for the last six months. The criteria for hyperactivity-

impulsivity mainly revolve around excessive motor activity, fidgeting and talkativeness (DSM Library). According to the subdivision of DSM diagnostic criteria, there are three presentations of attention-deficit hyperactivity disorder, including combined presentation, predominantly inattentive presentation and predominantly hyperactivity/impulsivity presentation. Combined presentation is diagnosed if the criteria for both inattention and hyperactivity are met for the past six months; predominantly inattentive presentation is diagnosed if only the criteria for inattention are met for the past six months, which is the inverse for predominantly hyperactivity/impulsivity presentation. While it is a widely accepted concept that environmental and genetic factors are accounted for the etiology of ADHD, the extent to which they influence this trait remains a question to be solved. Family and twin studies are extensively utilized to quantify the genetic and environmental impacts on ADHD. For instance, the difference between within-twin-correlation for a certain trait among monozygotic twins and dizygotic twins reflects the attribution of genetic influence to the trait, therefore enabling the estimation of heritability. Family studies, on the other hand, showcase the pattern of inheritance and familial aggregation, demonstrating the genetic risk for certain disorders among various degrees of relatives. Such properties of family and twin studies enable quantitative genetic researches to be carried out. Formatter will need to create these components, incorporating the applicable criteria that follow.

2. Etiology of Attention-deficit Hyperactivity Disorder and Its Induced Factors

With an approximate worldwide prevalence of 3.4%, attention-deficit hyperactivity disorder (ADHD) is one of the most common childhood-onset psychiatric disorders [3]. A substantial amount of twin and family studies have been conducted to inquire about the etiology of ADHD. Meta-analysis of twin studies on ADHD in childhood estimates the heritability to be between 70% and 80% [4], with the remaining variance explained by non-shared environmental influence. Moreover, studies rarely lay emphasis on shared environmental influence on ADHD due to its negligible magnitude [4]. The phenotypic symptoms of hyperactivity/impulsivity tend to become mild during the stage of early adolescence and stabilize in middle adolescence, which contrasts the case with inattention, which persists to be stable across the entire adolescence [3]. Similar findings have been stated in another study, which showcases the coexistence of both genetic stability and genetic innovation throughout life spans, suggesting both the characteristics of persistence and variance for phenotypic symptoms of ADHD [5].

2.1 Assessment of Familial Aggregation of Attention-deficit Hyperactivity Disorder

A considerable amount of family studies in the past two decades have successfully proven that the risk for ADHD is elevated by five-to-nine-fold for first-degree relatives of ADHD patients [6]. However, the majority of those studies are based on a small sample size and short-termed researches without sufficient follow-up investigations, therefore incapable of examining specific factors that can potentially impact the strength of familial aggregation. Moreover, although the genetic risk for first-degree relatives is clearly exhibited through data analysis in the previous studies, little is known for genetic risk among other degrees of relatives, such as half-siblings and cousins. All of these problems with preceding studies are properly solved in recent research using a Swedish population-based family study, which focused on promoting the precision in terms of the estimation for inheritance pattern that has been formerly reported [7].

Based on the cumulative incidences of ADHD diagnoses among both relatives of index persons with ADHD and index persons without ADHD (control group) during 20 years of research, two conclusions can be drawn. Firstly, relatives of ADHD patients are at higher risk compared to the general public, indicating the genetic influence on ADHD [7]. This can be easily perceived through by comparing cumulative incidences of ADHD in siblings and cousins of affected index persons (around 25.3% and 10.0%, respectively) to those among siblings and cousins of unaffected individuals (both around 3.6%). On top of that, the significant difference between incidences of ADHD among siblings of affected individuals (around 25.3%) and those among cousins of ADHD patients suggests that familial aggregation increases as genetic relatedness increases [7].

2.2 Assessment of Environmental Impacts on Attention-deficit Hyperactivity Disorder

Unlike genetic influence which escalates as the development of children, shared environmental influence gradually becomes insignificant as children grow into adults [3], which is also a property attributed to all shared environmental influences involved in various psychiatric disorders. On the other hand, the estimation of non-shared environmental influence that contributes to the difference between individuals tends to remain stable across age [8]. Additionally, shared and non-shared environmental influences are largely time-specific, meaning they are intertwined with emerging factors throughout children's development, whereas the same genes that induced the occurrence of ADHD retains its impact on this behavioral trait across age spectrum [3]. Furthermore, shared environmental influence can be correlated with ethnicity, which is exhibited in a study entitled "Genetic and environmental influences on attention deficit/ hyperactivity disorder symptoms in Chinese adolescents: a longitudinal twin study". This study discovers that shared environmental influences tend to be larger among Chinese ADHD patients compared to that among western samples, suggesting that collectivistic culture in Chinese society can reinforce the impact of shared environmental factors [3].

3. Co-occurrence Risk for Other Disorders among Patients with Attention-deficit Hyperactivity Disorder

3.1 Co-occurrence Risk for Other Psychiatric Disorders among Patients with Attention-deficit Hyperactivity Disorder

As attention-deficit/hyperactivity disorder (ADHD) is a complex mental illness that can be analyzed from different perspectives, considerable amounts of multidimensional research have addressed that ADHD has a wide range of associations with other psychiatric disorders. It has been shown that approximately 80 percent of patients with ADHD have at least one comorbid psychiatric disorder [9]. Although the overlapping symptoms of ADHD with other disorders have always been a typical challenge during the process of diagnosis, the advanced diagnostic system helped to disentangle them from one another and observe the traits independently, which eventually determine the accurate association in a multidirectional way. Among the observations, the most common coexisting psychiatric diseases include various types of mood disorders and substance use disorders [9].

The first notable mood disorder, in this case, is bipolar disorder. The comorbidity rates measured in the studies with large sample sizes were between 9.5% and 21.2%; and 5.1 % to 47.1 %, respectively, in the studies that test on relatively small sample sizes [10]. Such comorbidity also appeared in a Swedish population-based study conducted. Among the 54723 patients with bipolar disorder, about 2064 of them were also diagnosed with ADHD, which is 3.8%. Besides, by estimating the relative risk (RR) of coexistence of these two disorders, the individuals with ADHD had a substantially increased risk of getting affected by bipolar disorder (BPD). The RR value was 21.8, respectively [11]. Also, in terms of phenomenology, the connection was observed through common symptoms as well. The symptoms included distractibility, inattention, impulsivity, and talkativeness, etc. These common features further proved the association between ADHD and BPD, and these phenomena appeared more frequently in bipolar I over bipolar II and cyclothymia [10].

Other mood disorders that are frequently mentioned together in this conversation are depression and anxiety disorder. ADHD has a high prevalence of co-occurrence risk with major depression, with studies indicating that the commodity rates of ADHD with depression had a range between 18.6% and 53.3% [9]. Also, a survey that involved 575 patients diagnosed with ADHD tested their comorbidity with major depression. Among the 575 individuals, 123 are associated with major depressive disorder, corresponding to a prevalence rate of 21.39%, which dropped between the range mentioned above [12]. On the other hand, patients with ADHD also have increased risks of getting anxiety disorder than the general population. In the same study conducted by Ohnishi, they estimated a comorbidity rate of 12.17% among the 575 participants, which is relatively a significant number comparing other psychiatric disorders involved [12]. Besides the comorbidity rates, a study found that people who met the criteria for major depression and ADHD generally had lower quality of life based on self-rating

surveys. This is mainly due to the substantial economic burden of taking care of their disease [13]. Regarding anxiety disorder, a study also did an assessment from a clinical perspective. Patients with the coexistence of ADHD and anxiety seemed to have more severe anxiety symptoms, an earlier age of onset of anxiety disorder, and more frequently report on alcohol and drug abuse [14].

Furthermore, substantial research also found that ADHD is interconnected with substance use disorder (SUD). Common substances such as alcohol, nicotine, and cocaine, are found to be easily abused in many cases [15]. A study particularly investigating patients' dependency on nicotine through self-reports showcased that lifetime prevalence of smoking was more common in patients with ADHD. According to the data, earlier onset and higher rates of cigarettes smoking were also observed. All this evidence confirmed a strong connection between ADHD and substance dependence on nicotine, indicating severe addiction outcomes brought by SUD [16]. Also, it is found that ADHD could form a bidirectional relationship with SUD as the symptoms affected the degree of the severeness of one another. This bidirectional relationship also led to medical burden as it dramatically increased suicide attempts, the times people may seek hospitalization, and higher medical costs due to drug dependency and addiction [17]. Therefore, it is necessary to understand the induce factors of these comorbid impacts and their consequences in order to come with efficacious treatments.

3.2 Co-occurrence Risk for Several Physical Diseases among Patients with Attention-deficit Hyperactivity Disorder

The comorbidity of ADHD with other psychiatric disorders was shown in considerable amounts of studies. Moreover, some investigations suggest that there is an association between ADHD and physical diseases. Although the etiology of ADHD is mainly neurobiological, various studies have reported that patients who suffered from chronic diseases have a higher probability to have psychiatric disorders including ADHD [18].

One of the chronic diseases that show high prevalence in ADHD patients is cystic fibrosis (CF). Cystic fibrosis which has a prevalence of 7% in the general population is a chronic life-threatening disease [19]. The comorbidity of ADHD with CF is hypothesized due to the evidence that ADHD can cause functional impairment of the primary disease. It is believed that it is more difficult for CF patients with ADHD to control their primary disease. The rate of ADHD in CF patients was measured in a study with 122 patients and the results showed that 45% of the participants showed characteristics compatible with ADHD and 20 out of 122 participants showed characteristics that completely satisfy the DSM criteria [19]. The findings suggest a higher occurrence of ADHD in the population with CF which is compatible with another research that determines the rate of ADHD symptoms in children and adults. Among the 175 CF patients, 17.7% of them were found to satisfy ADHD criteria and both the children group and adult group showed a similar percentage (16%/18.9%) which is substantially higher than the percentage in the general population [18]. The results from these studies indicate a significantly higher rate of ADHD symptoms in CF patients compared to the general population which suggests comorbidity and moreover, higher inflammatory markers found in ADHD suggest that possible association may exist between ADHD and chronic inflammatory diseases [18].

Despite the chronic inflammatory diseases, studies have suggested the possible comorbidity between ADHD and allergic disease. Recent studies conducted on ADHD and allergic diseases showed comparable results. A large scaled population-based twin study that involved 1480 adolescent twin pairs investigated the longitudinal association between childhood asthma and two dimensions of ADHD [20]. The findings showed a significant increase in the risk of having one or more symptoms of hyperactivity-impulsivity in children with asthma (with OR (Odds Ratio) of 1.88 in 95% CI (confidence interval) and even more symptoms were found to appear in adolescents aged between 13-14 years with asthma. (OR 2.73, 95% CI) [20]. Researchers concluded the existence of an association between childhood asthma and ADHD with further evidence suggesting the phenotypic correlation between asthma and ADHD was due to genetic effects. In another study conducted by Chen comorbidity between ADHD and allergic diseases was confirmed. Among the 1000000-person sample population, 8201 participants were diagnosed with ADHD and comorbidity of allergic diseases was high in ADHD patients compared to control groups. Allergic diseases including asthma, allergic

rhinitis, atopic dermatitis all showed a significant odds ratio which further suggests the association between ADHD and allergic diseases [21]. In the same study, researchers further suggested the possible comorbidity between ADHD and autoimmune diseases. Despite the lower comorbidity compared with allergic diseases, autoimmune diseases for instance ankylosing spondylitis (AS), and autoimmune thyroid disease both showed significantly OR compared to control groups [21].

Although the comorbidity between ADHD and autoimmune disease was suggested by various studies, the underlying mechanism of ADHD in autoimmune diseases still remains unclear which may explain the inconsistency between results between recent studies and studies conducted in the 1990s. All these studies suggest that ADHD not only is associated with psychiatric diseases but can functionally impair many physical diseases as well. Due to the fact that the mechanism of ADHD played in several physical diseases still remains indistinct, further researches should be conducted based on the comorbidity discovered.

4. Conclusion

Our paper showed that the etiology of Attention Deficit Disorder is mainly genetic related. Shared environment influence compared to heritability plays a less significant role as the children mature into adults, however, additional evidence showed that the effect of shared environmental influence on ADHD could be due to its correlation with ethnicity. Moreover, depressive disorders and anxiety disorders together with substance use disorders were found to have a high co-occurrence rate with ADHD. Despite the co-morbidity between ADHD and psychiatric disorders, ADHD can also impair patients' ability to handle their primary physical disorders which were revealed by the high co-occurrence rate of ADHD in patients with chronic diseases, inflammatory diseases and autoimmune diseases. From a clinical perspective, our paper may provide more insight into the diagnosis and intervention of ADHD. Due to the high co-occurrence of ADHD with other psychiatric disorders, more accurate diagnostic criteria are required to distinguish ADHD from other behavior disorders. Moreover, the co-occurrence feature of ADHD requires caregivers to have expertise in not only ADHD but other psychiatric disorders as well. Although the impairment of ADHD on academic performance and social interaction has been widely recognized by society, educational remediation and cognitive behavior support for ADHD patients who suffer from other chronic diseases are scarce. The intervention strategy for each patient needs to be considered separately which requires extra training for caregivers. As a serious heterogeneous behavior disorder that has a high prevalence around the world, the diagnosis and intervention of ADHD must be dealt with more effort.

References

- [1] K.W. Lange, S. Reichl, K.M. Lange, L. Tucha, and O. Tucha, "The history of attention deficit hyperactivity disorder," *Attention deficit and hyperactivity disorders*, 2010, vol. 2, pp. 241-255.
- [2] D.J. Morris-Rosendahl, and M.A. Crocq, "Neurodevelopmental disorders-the history and future of a diagnostic concept," *Dialogues in clinical neuroscience*, 2020, vol. 22, pp. 65-72.
- [3] G.V. Polanczyk, G.A. Salum, L.S. Sugaya, A. Caye, L.A. Rohde, "Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents," *J Child Psychol Psychiatry*, 2015, vol. 56, pp. 345-365.
- [4] M.A. Nikolas, S.A. Burt, "Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: A meta-analysis," *Journal of Abnormal Psychology*, 2010, vol. 119, pp. 1-17.
- [5] Z. Chang, P. Lichtenstein, P.J. Asherson, and H. Larsson, "Developmental twin study of attention problems: High heritabilities throughout development," *JAMA Psychiatry (Chicago, Ill.)*, 2013, vol. 70, pp. 311-318.

- [6] W. Chen, K. Zhou, P. Sham, B. Franke, J. Kuntsi, D. Campbell, and P. Asherson, "DSM-IV combined type ADHD shows familial association with sibling trait scores: A sampling strategy for QTL linkage," *American Journal of Medical Genetics, Part B, Neuropsychiatric Genetics*, 2008, vol. 147B, pp. 1450-1460.
- [7] Q. Chen, I. Brikell, P. Lichtenstein, E. Serlachius, R. Kuja-Halkola, S. Sandin, and H. Larsson, "Familial aggregation of attention-deficit/hyperactivity disorder," *Journal of Child Psychology and Psychiatry*, 2017, vol. 58, pp. 231-239.
- [8] Z. Chang, P. Lichtenstein, P.J. Asherson, and H. Larsson, "Developmental twin study of attention problems: high heritabilities throughout development," *JAMA psychiatry*, 2013, vol. 70, pp. 311-318.
- [9] M.A. Katzman, T.S. Bilkey, P.R. Chokka, A. Fallu, and L.J. Klassen, "Adult ADHD and comorbid disorders: Clinical implications of a dimensional approach," *BMC Psychiatry*, 2017, vol. 17, pp. 302-302.
- [10] A.P. Wingo, S.N. Ghaemi, "A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder," *The journal of clinical psychiatry*, 2007, vol. 68, pp. 1776-1784.
- [11] J. Song, E. Bergen, R. Kuja-Halkola, H. Larsson, M. Landen, and P. Lichtenstein, "Bipolar disorder and its relation to major psychiatric disorders: A family-based study in the Swedish population," *bipolar disorders*, 2015, vol. 17, pp. 184-193.
- [12] T. Ohnishi, H. Kobayashi, T. Yajima, T. Koyama, and K. Noguchi, "Psychiatric comorbidities in adult attention-deficit/hyperactivity disorder: Prevalence and patterns in the routine clinical setting," *Innovations in Clinical Neuroscience*, 2019, vol. 16, pp. 11-16.
- [13] R.S. McIntyre, S.H. Kennedy, J.K. Soczynska et al, "Attention-deficit/hyperactivity disorder in adults with bipolar disorder or major depressive disorder: Results from the international mood disorders collaborative project," *Primary care companion to the Journal of clinical psychiatry*, 2010, vol. 12.
- [14] C. Mancini, M. Van Ameringen, J.M. Oakman, and D. Figueiredo, "Childhood attention-deficit/hyperactivity disorder in adults with anxiety disorders," *Psychological Medicine*, 1999, vol. 29, pp. 515-525.
- [15] L.J. Klassen, T.S. Bilkey, M.A. Katzman, and P. Chokka, "Comorbid attention-deficit/hyperactivity disorder and substance use disorder: Treatment considerations," *Current Drug Abuse Reviews*, 2012, vol. 5, pp. 190-198.
- [16] T.E. Wilens, M. Vitulano, H. Upadhyaya, J. Adamson, R. Sawtelle, L. Utzinger, and J. Biederman, "Cigarette smoking associated with attention deficit hyperactivity disorder," *The Journal of Pediatrics*, 2008, vol. 153, pp. 414-419.
- [17] J. Martinez-Raga, N. Szerman, C. Knecht, R. de Alvaro, "attention deficit hyperactivity disorder and dual disorders. Educational needs for an underdiagnosed condition," *Int J Adolesc Med Health*, 2013, vol. 25, pp. 231-43.
- [18] M. Cohen-Cymerknoh, T. Tanny, O. Breuer, H. Blau, H. Mussaffi, D. Kadosh, "Attention deficit hyperactivity disorder symptoms in patients with cystic fibrosis," *Journal of Cystic Fibrosis*, 2018, vol. 17, pp. 281-285.
- [19] M. Cohen-Cymerknoh, T. Tanny, H. Blau, D. Kadosh, H. Mussaffi, V. Nir, "300 Prevalence and characteristics of attention deficit hyperactivity disorder (ADHD) in patients with cystic fibrosis (CF)," *Journal of Cystic Fibrosis*, 2015, vol. 14, S134.

[20] N. Mogensen, H. Larsson, C. Lundholm, and C. Almqvist, "Association between childhood asthma and ADHD symptoms in adolescence a prospective population-based twin study," *Allergy*, 2011, vol. 66, pp. 1224-1230.

[21] M.H. Chen, T.P. Su, Y.S. Chen, J.W. Hsu, K.L. Huang, W.H. Chang, T. J. Chen, and Y.M. Bai, "Comorbidity of allergic and autoimmune diseases among patients with ADHD," *Journal of Attention Disorders*, 2016, vol. 21, pp. 219-227.