

**Comorbidity of ADHD and Major Depressive Disorder:  
Exploring Biological and Interpersonal Factors**

Tu-Minh H. Bui

University of California, Davis

### **Abstract**

This literature review aims to synthesize and contextualize current research on ADHD and MDD across biological and interpersonal factors to assess how the two interplay. This is accomplished by assessing genetic disposition and neurobiological underpinnings alongside parent-child relationships and peer interactions to address interpersonal factors. The main queries used to search for peer-reviewed journal articles were “ADHD and depression” and “childhood ADHD and depression” across four databases: APA PsycARTICLES, PubPsych, PubMed, and MIT Cognet. Findings reveal that genetic factors contributing to hyperactivity and inattention also influence depressive traits. Neuroimaging studies revealed that individuals with ADHD and MDD comorbidity exhibit neurological structural and functional abnormalities. Environmentally, parents of children with ADHD are more likely to have children who develop MDD if they have poor mental health. Additionally, children with ADHD are more likely to be socially rejected by their peers, affecting their self-esteem and thus increasing the likelihood of developing MDD later in life. Understanding how these factors interplay is critical in accurately assessing the biological-environmental conditions of children with ADHD to determine their risk of developing MDD. As a result of these findings, clinicians should be vigilant in screening for depressive symptoms in individuals diagnosed with ADHD to facilitate early intervention, such as psychosocial training and social skills development, to reduce the likelihood of MDD later in life.

*Keywords:* ADHD, Major Depressive Disorder, Comorbidity, depression, mental health disorder, developmental disorder

### **Introduction**

Attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD) regularly co-occur, with research indicating that individuals with ADHD are at an elevated risk of developing depression. This comorbidity poses an issue in diagnosing and treating either disorder due to their overlapping symptoms and potential misattribution of depressive traits. Furthermore, ADHD symptoms are likely to mask symptoms of depression, delaying proper intervention (Biederman et al., 2021). Current research has identified contributors responsible for the relationship between ADHD and MDD, but few have assessed their combined influence. This literature review aims to synthesize recent findings on the biological and interpersonal factors contributing to this interaction. Biological factors will examine the genetic predisposition and neurobiological underpinnings of the disorders, and interpersonal factors will be investigated through parent-child as well as peer-child relationships.

### **Methods**

The main queries used to search for peer-reviewed journal articles were “ADHD and depression” and “childhood ADHD and depression”. These queries were used across four databases: APA PsycARTICLES, which yielded 176 results, PubPsych, which yielded 2354 results, PubMed, which yielded 1262 results, and MIT Cognet, which yielded 127 results. The specific population of interest for this paper was children from the age group birth-12 years old. Studies focusing on specific demographic subsets (e.g, race, sexual orientation) were excluded to maintain generalizability. Peer-reviewed studies published within the last five years were prioritized, with exceptions for papers within the last 10 years if highly relevant. Relevancy was determined based on the criteria that the study directly observed the comorbidity between ADHD and MDD in the context of four factors: genetic, neurobiological, parent-child relationships, and

interpersonal peer relationships. These criteria were applied to the findings using the search manual and automatic filters. Additionally, “genetic”, “neurobiological”, “parent”, and “peer” were applied to queries on all databases to reduce the remaining articles. As a result, there were a remaining 27 relevant findings from APA PsycARTICLES, 584 from PubPsych, 276 from PubMed, and 37 from MIT CogNet. From these findings, 12 were selected based on the following criteria: seminal work, methodological rigor, diversity of perspectives, and relevance.

## **Results**

### **Biological Factors**

Research has identified significant biological contributions to comorbid ADHD and MDD, with studies assessing genetic and neurobiological factors. The combined genetic predisposition and brain network abnormalities increase the likelihood of developing both disorders.

### ***Genetic Factors***

Studies examining genetic factors have indicated a hereditary component in the comorbidity between ADHD and MDD. Through longitudinal analysis, studies following children with ADHD were found to reveal that they were at an elevated risk of later developing depression in adulthood, estimated to be around 35% more likely than neurotypical peers. These results reveal that the vulnerabilities affecting Further Mendelian Randomization Analysis revealed that individuals with genetic predisposition to ADHD were at a 21% increased risk of developing MDD, although these risks were lower when applied to a broader definition of depression (Riglin et. al, 2020).

Twin studies across genetically identical monozygotic twin pairs and dizygotic twin pairs, who share 50% of their genes, have revealed heritability estimates between 60-80% for ADHD

and 40-50% for MDD. These significant rates are indicative of overlapping genetic variants between the disorders, which are only as prevalent as they are in both twins due to the heritability of the conditions (Faraone & Larsson, 2019). Other twin studies revealed a significant positive correlation between hyperactivity/inattention traits and depressive traits-in both boys and girls. Hyperactivity/inattention is a common trait used to code for ADHD, meanwhile depressive traits were used to code for MDD. Through bivariate structural equation modeling, researchers were able to isolate the genetic factors associated with both traits, revealing a correlation of 0.77 for boys and 0.67 for girls. These findings suggest that genetic factors contributing to ADHD significantly influence depressive traits (Cole et. al, 2009).

Dopamine-related genes (e.g, DRD4 and DAT1) as well as serotonin-regulating genes (e.g, 5-HTTLPR) are known to be linked to ADHD and depression due to their roles in behavior, attention, and mood regulation. Polymorphisms and deficits in these genes interfere with their ability to modulate these traits and have been implicated in increased susceptibility to both disorders (Demotnis et. al, 2019).

### ***Neurobiological Factors***

Neuroimaging studies and neurochemical observations have revealed structural and functional abnormalities in individuals with ADHD and MDD comorbidity. The prefrontal cortex is a crucial area in the brain for attention and impulse control, and the amygdala regulates emotional responses. FMRI studies have shown reduced activity in both of these areas in individuals with ADHD and MDD (Shaw et al., 2014). These neural deficits lead to reduced attention and impulse control as well as weakened emotional responses. This induces an environment that fosters ADHD and MDD symptoms, due to increased struggles with impulse control and heightened emotional sensitivity.

Event-related potentials (ERPs) were used to analyze attention and behavioral inhibition in individuals with ADHD and MDD comorbidity. The findings revealed weakened neural responses during inhibitory control tasks compared to healthy controls. The P3 amplitude, a neural marker of attention allocation, was reduced in these individuals, resulting in deficits in cognitive processing, attention, and inhibitory control—all symptoms of ADHD. The Nogo N2 latency, which reflects how quickly the brain detects a need for inhibition, was significantly longer in the MDD + ADHD group ( $M = 400$  ms) compared to the control group ( $M = 350$  ms,  $p < 0.05$ ) (Kim et al., 2020). This delay in the detection of the need for inhibition is another factor that manages inhibitory control. Moreover, the study reported heightened neural activity related to error detection. This suggests that comorbid ADHD and MDD individuals have heightened sensitivity to mistakes, which is correlated with rumination and negative self-perception, both contributors to depression (Kim et al., 2020).

### **Interpersonal Factors**

The factors influencing the comorbidity of ADHD and MDD extend beyond biological factors. Current research indicates that children's interpersonal relationships, particularly parent-child relationships and peer interactions, largely influence the risk of developing MDD in children diagnosed with ADHD.

#### ***Parent-Child Relationships***

Parents actively foster environments for their children that shape their mindsets and influence their mental states. Studies examining the role of parenting in the development of depression in children with ADHD revealed that inconsistent parenting, high parental criticism, and low emotional warmth result in emotional instability, low self-esteem, and feelings of neglect in children with ADHD. These factors increase the likelihood of developing depression

later in life (Chronis-Tuscano et al., 2019). Strained relationships with their parents may be a consequence of parents struggling to manage their child's ADHD symptoms, leading to elevated levels of parent-child rejection and hostility. Negative emotional climate at home is associated with a higher risk of developing internalizing disorders, including MDD (Lifford et al., 2008).

Parental psychopathology is strongly correlated with a child's development of comorbid ADHD and depression. Foremost, parental ADHD is independently associated with externalizing symptoms, such as aggression and defiance, and parental MDD with internalizing symptoms, such as depression, in children with ADHD (Chronis-Toscano et al., 2019). This reveals that having a parent with either condition can lead to heightened emotional dysregulation, which can amplify ADHD and depression symptoms.

Children with comorbid ADHD and MDD were more likely to have mothers with a history of depression (Vance & Lee, 2016). This may be due to a combination of heritability and emotional climate factors. Related research investigated mother-child relationships to reveal that mothers with MDD were more likely to have negative interactions with their children, contributing to ADHD symptoms in their children in addition to the development of depressive symptoms (Martinez-Torteya & Doyle, 2013). Overall, high-conflict parent-child relationships significantly predict depression in children with ADHD.

### ***Interpersonal Peer Relationships***

In addition to their parents, young children often interact with peers. Consequently, the quality of these relationships plays a significant role in the development of MDD in children with ADHD. In particular, children with ADHD struggle with impulsivity, hyperactivity, and inattention, making it difficult for them to navigate social interactions and leading to increased levels of social rejection and low peer acceptance (Biederman et al., 2008). These peer

difficulties contribute to feelings of isolation and undermine social identity, facilitating the relationship between childhood ADHD and adolescent depression. As a result, children with ADHD are more likely to experience bullying victimization than their counterparts without ADHD, which is strongly associated with increased depressive symptoms in children with ADHD (Sibley & Yule, 2015). Studies observing the social contextual factors in peer relationships of children with ADHD emphasize the importance of peer acceptance and high-quality friendships in their social success. Accordingly, children with ADHD and healthy relationships with their peers are less likely to experience social rejection, reducing the risk of developing MDD (Harrison & Hodge, 2014).

Another study utilizing data from the Avon Longitudinal Study of Parents and Children (ALSPAC) found that childhood ADHD symptoms were correlated with higher MDD symptoms in adolescence. Through mediation analysis, researchers evaluated the causality of peer problems and comorbid ADHD and MDD. Structural equation modeling and regression-based mediation analysis revealed that peer problems were accountable for around 14.68% of the association between ADHD and MDD (Powell et al., 2020). Findings could be attributed to ADHD symptoms interfering with social interactions and leading to increased peer problems. Peers perceived inattention symptoms in children with ADHD as disinterest and unreliability, leading to social exclusion and low peer engagement, whereas hyperactivity is seen as annoying and/or overwhelming, and impulsivity is seen as unpredictable and aggressive. Ultimately, the symptoms of ADHD in children increase social rejection by peers, which leads to lowered self-esteem and exacerbates depressive symptoms later in life.

### **Discussion**

The comorbidity of ADHD and MDD is influenced by biological and interpersonal variables across genetic and neurobiological factors, as well as parent-child and peer-child relationships. Studies have shown that genetic heritability and neurobiological abnormalities are causal factors in the comorbid relationship between ADHD and MDD.

However, these biological factors interact with environmental stressors to further exacerbate depressive symptoms. Biological predisposition to either condition makes individuals mentally vulnerable, increasing the importance of establishing healthy emotional environments through interpersonal relationships. This is significant because Strained relationships with parents and peers result in intensified effects on individuals with ADHD, who already have dopamine and/or serotonin deficiencies.

Understanding how these factors interplay is critical in thoroughly assessing the biological-environmental conditions of children with ADHD to determine their risk of developing MDD. As a result of these findings, clinicians should be vigilant in screening for depressive symptoms in individuals diagnosed with ADHD to facilitate early intervention, such as psychosocial training and social skills development, to reduce the likelihood of MDD later in life. By comprehensively combining biological insights with environmental context, clinicians can develop more effective, personalized treatment plans to address the needs of affected individuals.

### References

- Biederman, J., Petty, C. R., Monuteaux, M. C., & Faraone, S. V. (2008). What explains the link between childhood ADHD and adolescent depression? Investigating the role of peer relationships and academic attainment. *Journal of the American Academy of Child & Adolescent Psychiatry, 47*(7), 717–725. <https://doi.org/10.1097/CHI.0b013e3181742546>
- Chronis-Tuscano, A., Clarke, T., & MacDonald, K. (2019). Parenting and depression in children with ADHD: A review of the literature. *Journal of Attention Disorders, 23*(10), 1061–1071. <https://doi.org/10.1177/1087054718774178>
- Cole, J., Ball, G., Smith, S. M., & Bullmore, E. T. (2009). Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(11), 1094-1101. <https://doi.org/10.1097/CHI.0b013e3181b6b45b>
- Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Halmøy, A., Nijmeijer, S. E., ... & Faraone, S. V. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics, 51*(1), 63–75. <https://doi.org/10.1038/s41588-018-0269-7>
- Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *\*Molecular Psychiatry, 24\**(5), 562–575. <https://doi.org/10.1038/s41380-019-0131-7>
- Harrison, J. R., & Hodge, C. W. (2014). The importance of social contextual factors in peer relationships of children with ADHD. *Journal of Attention Disorders, 18*(7), 652–663. <https://doi.org/10.1177/1087054713486023>

Kim, J. W., Park, K. H., Cheon, K. A., Kim, B. N., Cho, S. C., & Hong, Y. C. (2020).

Event-related potentials in patients with major depressive disorder and comorbid adult attention-deficit hyperactivity disorder. *Psychiatry Investigation*, *17*(3), 195-203.

<https://doi.org/10.30773/pi.2019.0111>

Powell, V., Riglin, L., Hammerton, G., Eyre, O., Martin, J., Anney, R., Thapar, A., & Rice, F.

(2020). What explains the link between childhood ADHD and adolescent depression?

Investigating the role of peer relationships and academic attainment. *European Child & Adolescent Psychiatry*, *29*(11), 1581–1591. <https://doi.org/10.1007/s00787-019-01432-0>

Riglin, L., Collishaw, S., Dalsgaard, S., & Thapar, A. (2020). The familial risk of ADHD and the

role of genetics in attention-deficit hyperactivity disorder. *JAMA Psychiatry*, *77*(1),

14-24. <https://doi.org/10.1001/jamapsychiatry.2019.3145>

Shaw, P., Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion dysregulation in attention

deficit hyperactivity disorder. *American Journal of Psychiatry*, *171*(3), 276–293.

<https://doi.org/10.1176/appi.ajp.2013.13070966>

Sibley, M. H., & Yule, A. M. (2015). Bullying and depression in youth with ADHD: A

systematic review. *Journal of Attention Disorders*, *19*(7), 578–586.

<https://doi.org/10.1177/1087054714530450>

Sudre, G., Leonard, M. E., Shaw, P., & Posner, J. (2022). The genetic and neurobiological basis

of comorbidity between attention-deficit/hyperactivity disorder and mood disorders.

*Frontiers in Psychiatry*, *13*, 949375. <https://doi.org/10.3389/fpsy.2022.949375>