# Global Gender Disparities in Adolescents' Affective Disorders: A Neuroendocrine Systematic Review

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**ABSTRACT**: Affective disorders pose a global health challenge and gender disparity. This review explores neuroendocrine mechanisms in adolescent affective disorders, revealing elevated cortisol and thyrotropin levels, puberty's impact, and frontolimbic neurocircuitry involvement. Gender and epigenetic factors within HPA axis genes highlight the need for interventions. Understanding these can inform strategies for stress reduction and treatments, emphasizing the vulnerability of adolescent girls to affective disorders and the importance of gender-targeting approaches in diagnosis and intervention.

## 1. INTRODUCTION

Affective disorders, also known as mood disorders, are considered a significant global health concern. These disorders are described by marked disruptions in emotions and include major depressive disorder (MDD), bipolar disorder (BD), and persistent disruptive disorder (PDD). Today, a notable gender disparity exists within these disorders, with very little information known about the neurobiological underpinnings of this gap. Epidemiological data consistently shows higher rates of affective disorders among females with twice as many women as men experiencing depression (Walther et al., 2017).

Adolescent populations are particularly impacted by the affective disorders with the adolescent girls showing one of the highest rates among this population. Stress exposure during the developmental stage is a large risk factor for depression among the adolescent girls (Gobinath et al., 2015). In addition, the dysfunction between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axis is also present in adolescents with MDD (Hirtz et al., 2021). The adolescents with MDD exhibit distinct neuroendocrine patterns, that includes elevated cortisol and thyrotropin levels (Hirtz et al., 2021). This disparity in endocrine functioning between adolescents and adults with MDD can be explained through age-related factors (Hirtz et al., 2021). Additionally, the interplay between neuroendocrine stress responses and frontolimbic neurocircuitry plays a large role (Thai et al., 2021). This connection reveals how frontolimbic resting-state functional connectivity (RSFC) patterns influence HPA axis functioning, offering insights into the potential development of treatments (Thai et al., 2021). This systematic review also unravels gender-specific nuances in symptoms, emphasizing the importance of gender-tailored approaches to diagnosis and treatment (Eng et al., 2023). Epigenetic factors within HPA axis genes are significant as well, highlighting their role in the onset of affective disorders in adolescent girls (Humphreys et al., 2019). Furthermore, the role of serotonin

dysregulation and its connection to suicidal and depressive behaviors is a notable factor (Ghaziuddin et al., 2014).

The neuroendocrine response observed in teen depression and suicide, compared to adults, as well as in females compared to males, calls for targeted interventions (Pandey et al., 2019). By examining these findings, this review offers a comprehensive understanding of gender disparities in adolescents' affective disorders, highlighting key neuroendocrine mechanisms and shedding light on potential targets for interventions (Thai et al., 2021).

## 2. METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to explore the neuroendocrine differences between male and female's affective disorders.

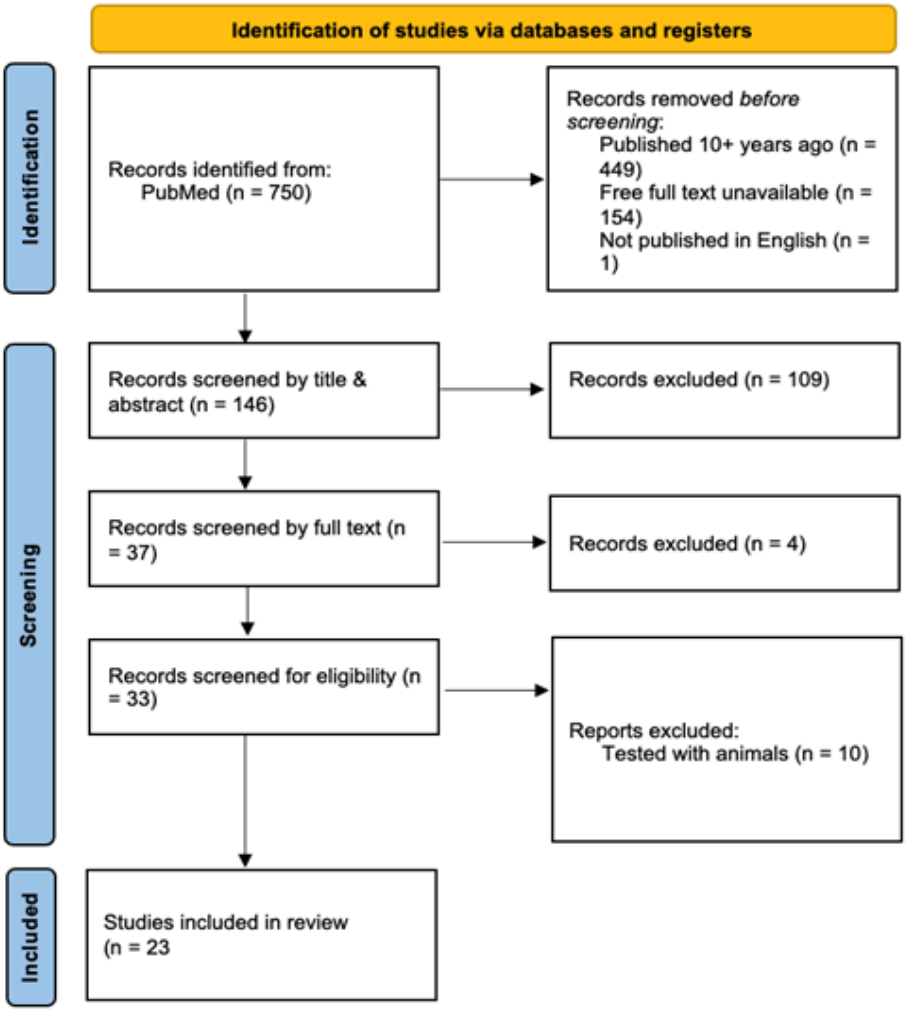


**Figure 1.** *PRISMA Flow Diagram of Methods*

A comprehensive search was conducted on the database PubMed using the keywords: ((mood disorder) OR (affective disorder) OR (depression) OR (MDD) OR (bipolar disorder)) AND (neuroendocrine) AND ((gender) OR (sex) OR (female) OR (girl) OR (woman) OR (women) OR (male) OR (boy) OR (man) OR (men)) AND ((teenage) OR (adolescent) OR (youth)). This yielded 750 results. To focus on recent insights, only studies published in the last 10 years (2013-2023) were included, leading to the exclusion of 449 papers. 154 articles were excluded due to not having a full version available. 1 article was excluded as it was not published in English. Next, the 146 remaining articles were screened by title and abstract for relevance to the topic of this systematic review, with 109 being excluded. The remaining 37 were thoroughly examined, and 4 were excluded due to lack of relevance. Finally, of the 33 remaining studies, 10 were excluded as they were tested on animals rather than humans. In total, 23 articles were included in this systematic review.

## 3. RESULTS

Findings from a variety of studies explained the complex relationship between neuroendocrine factors and affective disorders during the critical developmental period, adolescence. Across the included studies, statistical synthesis showed multiple distinctive patterns. Adolescents exposed to stress during this phase displayed an immensely higher risk of developing affective disorders (Gobinath et al., 2015). The cortisol reactivity patterns observed in adolescents with affective disorders were also notable. Many exhibited weakened cortisol responses, a phenomenon consistent with more severe depressive symptoms, displaying a clear relationship between symptomatology and neuroendocrine functioning (Morris et al., 2017).

Furthermore, the interaction between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axes, which regulate stress response, brain development, and more, displayed intriguing findings. Adolescents with affective disorders had elevated cortisol and thyrotropin levels, indicating dysfunctions within both axes (Hirtz et al., 2021). Additionally, a linear relationship between thyrotropin and cortisol levels suggested the possible independent functioning of these axes, particularly in those with elevated cortisol levels (Hirtz et al., 2021).

The impact of puberty and maturational processes on the neuroendocrine system in adolescents was also evident. The presence and activity of puberty hormones played a large role in shaping the neuroendocrine factors of affective disorders in adolescents (Hirtz et al., 2021).

Additionally, frontolimbic neurocircuitry showed a significant role. Frontolimbic resting-state functional connectivity (RSFC) patterns impacted HPA axis functioning. Dysfunctions in the HPA axis stress response and frontolimbic neurocircuitry were commonly observed in affective disorders (Thai et al., 2021). The amygdala's association with stress activation and its hyperactivity's link to MDD and other affective disorders added a further level of understanding. Reduced activity in the medial prefrontal cortex, which regulates the HPA axis, played yet another role in the complex neuroendocrine aspects of adolescent affective disorders (Thai et al., 2021).

The difference in rates between females and males' affective disorders were also explained by an examination on their gender differences. Stress response emerged as a major reason for the disparities. Females have consistently higher rates of MDD and other affective disorders than men (Walther et al., 2017). Stress affects males and females differently at different phases of life, including prenatal, postnatal, and adolescent periods (Gobinath et al., 2015). Results of the Trier Social Stress Test (TSST), which induces stress and depressive-like symptoms, showed different HPA axis responses through the varying levels of ACTH and cortisol between males and females, a defining factor for the gender disparities in affective disorders (Stephens et al., 2016).

Epigenetic markers within specific CpG sites of HPA axis genes also contribute significantly to the risk of developing affective disorders in adolescent girls especially. Genes such as NR3C1, CRH, CRHR1, and CRHR2 showed associations with the affective disorders across adolescence and young adulthood in females (Humphreys et al., 2019). DNA methylation levels within these sites showed consistency with the onset of affective disorders after controlling for genetic variation within these genes (Humphreys et al., 2019). These findings highlighted the influence of epigenetic factors, specifically DNA methylation, in predicting the development of affective disorders. Variations in DNA methylation within these specific genes related to the HPA axis suggested the onset of affective disorders in adolescent girls, further emphasizing the gender-specific nature of these conditions (Humphreys et al., 2019).

## 4. DISCUSSION

The comprehensive understanding of affective disorders and their wide prevalence in the population of adolescent females in these studies can help with multiple potential uses for research and clinical practice in the medical and psychological fields. Recognizing the vulnerability of adolescents, particularly girls, to affective disorders calls for new intervention and targeting strategies that focus on stress reduction. Interventions targeting the commonly dysregulated HPA and HPT axes and frontolimbic neurocircuitry can also help mitigate the impact of these disorders.

Furthermore, the gender differences exhibited highlight the importance of gender-tailored approaches to the diagnoses and treatments of affective disorders. Medical professionals must consider the distinct stress responses and hormonal influences that lead to the higher prevalence of affective disorders in females. Epigenetic markers within HPA axis genes also provide a new pathway for accurate and predictable identifications and interventions, particularly for adolescent girls.

Future research must dive deeper into the complex interactions between the neuroendocrine systems, stress/symptoms, and gender surrounding affective disorders. Tracking the neurobiology of adolescents through puberty and beyond can provide valuable insights into the developmental underpinnings of these disorders.

## 5. CONCLUSIONS

Adolescent girls are at particularly high risk of affective disorders. Factors behind this include the differing stress responses, maturational processes, and genetics between males and females and the age group of adolescents. Targeting these specific causes in future interventions and treatments can lower the risk adolescent girls are at for affective disorders.

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## REFERENCES

Beauchaine, T. P., Crowell, S. E., & Hsiao, R. C. (2014). Post-dexamethasone cortisol, self-inflicted injury, and suicidal ideation among depressed adolescent girls. *Journal of Abnormal Child Psychology*, *43*(4), 619–632. https://doi.org/10.1007/s10802-014-9933-2

Carol, E. E., Spencer, R. L., & Mittal, V. A. (2016). Sex differences in morning cortisol in youth at ultra-high-risk for psychosis. *Psychoneuroendocrinology*, *72*, 87–93. https://doi.org/10.1016/j.psyneuen.2016.06.013

Colich, N. L., Kircanski, K., Foland-Ross, L. C., & Gotlib, I. H. (2015). HPA-axis reactivity interacts with stage of pubertal development to predict the onset of depression. *Psychoneuroendocrinology*, *55*, 94–101. https://doi.org/10.1016/j.psyneuen.2015.02.004

Eng, A. G., Phan, J. M., Shirtcliff, E. A., Eisenlohr-Moul, T. A., Goh, P. K., & Martel, M. M. (2023). Aging and pubertal development differentially predict symptoms of ADHD, depression, and impairment in children and adolescents: An eight-year longitudinal study. *Research on Child and Adolescent Psychopathology*, *51*(6), 819–832. https://doi.org/10.1007/s10802-023-01030-7

Ghaziuddin, N., King, C. A., Welch, K., & Ghaziuddin, M. (2014). Depressed suicidal adolescent males have an altered cortisol response to a pharmacological challenge. *Asian Journal of Psychiatry*, *7*, 28–33. https://doi.org/10.1016/j.ajp.2013.10.005

Giletta, M., Calhoun, C. D., Hastings, P. D., Rudolph, K. D., Nock, M. K., & Prinstein, M. J. (2014). Multi-level risk factors for suicidal ideation among at-risk adolescent females: The role of hypothalamic-pituitary-adrenal axis responses to stress. *Journal of Abnormal Child Psychology*, *43*(5), 807–820. https://doi.org/10.1007/s10802-014-9897-2

Gobinath, A. R., Mahmoud, R., & Galea, L. A. M. (2015). Influence of sex and stress exposure across the lifespan on endophenotypes of depression: Focus on behavior, glucocorticoids, and Hippocampus. *Frontiers in Neuroscience*, *8*. https://doi.org/10.3389/fnins.2014.00420

Hirtz, R., Libuda, L., Hinney, A., Föcker, M., Bühlmeier, J., Antel, J., Holterhus, P.-M., Kulle, A., Kiewert, C., Hebebrand, J., & Grasemann, C. (2021). Lack of Evidence for a Relationship Between the Hypothalamus-Pituitary-Adrenal and the Hypothalamus-Pituitary-Thyroid Axis in Adolescent Depression. *Front Endocrinol (Lausanne)*. https://doi.org/10.3389/fendo.2021.662243

Humphreys, K. L., Moore, S. R., Davis, E. G., MacIsaac, J. L., Lin, D. T., Kobor, M. S., & Gotlib, I. H. (2019). DNA methylation of HPA-axis genes and the onset of major depressive disorder in adolescent girls: A prospective analysis. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0582-7

Kircanski, K., Sisk, L. M., Ho, T. C., Humphreys, K. L., King, L. S., Colich, N. L., Ordaz, S. J., & Gotlib, I. H. (2019). Early life stress, cortisol, frontolimbic connectivity, and depressive symptoms during puberty. *Development and Psychopathology*, *31*(3), 1011–1022. https://doi.org/10.1017/s0954579419000555

Kortesluoma, S., Korhonen, L. S., Pelto, J., Tuulari, J. J., Karlsson, L., & Karlsson, H. (2022). Age and sex differences in the cortisol stress reactivity and recovery among infants exposed to prenatal psychological distress. *Psychoneuroendocrinology*, *135*. https://doi.org/10.1016/j.psyneuen.2021.105580

Koss, K. J., Cummings, E. M., Davies, P. T., & Cicchetti, D. (2016). Patterns of Adolescent Regulatory Responses During Family Conflict and Mental Health Trajectories. *Journal of Research on Adolescence*, *27*(1), 229–245. https://doi.org/10.1111/jora.12269

LeMoult, J., Ordaz, S. J., Kircanski, K., Singh, M. K., & Gotlib, I. H. (2015). Predicting first onset of depression in young girls: Interaction of diurnal cortisol and negative life events. *Journal of Abnormal Psychology*, *124*(4), 850–859. https://doi.org/10.1037/abn0000087

Lopez-Duran, N., McGinnis, E., Kuhlman, K., Geiss, E., Vargas, I., & Mayer, S. (2015). HPA-axis stress reactivity in youth depression: Evidence of impaired regulatory processes in depressed boys. *Stress*, *18*(5), 545–553. https://doi.org/10.3109/10253890.2015.1053455

Lu, Q., Pan, F., Ren, L., Xiao, J., & Tao, F. (2018). Sex differences in the association between internalizing symptoms and hair cortisol level among 10-12 year-old adolescents in China. *PLOS ONE*, *13*(3). https://doi.org/10.1371/journal.pone.0192901

Morris, M. C., Kouros, C. D., Mielock, A. S., & Rao, U. (2017). Depressive symptom composites associated with cortisol stress reactivity in adolescents. *Journal of Affective Disorders*, *210*, 181–188. https://doi.org/10.1016/j.jad.2016.12.023

Owens, S. A., Helms, S. W., Rudolph, K. D., Hastings, P. D., Nock, M. K., & Prinstein, M. J. (2018). Interpersonal Stress Severity Longitudinally Predicts Adolescent Girls' Depressive Symptoms: the Moderating Role of Subjective and HPA Axis Stress Responses. *Journal of Abnormal Child Psychology*, *47*(5), 895–905. https://doi.org/10.1007/s10802-018-0483-x

Pandey, G. N., Rizavi, H. S., Bhaumik, R., & Ren, X. (2019). Increased protein and mrna expression of corticotropin-releasing factor (CRF), decreased CRF receptors and CRF binding protein in specific postmortem brain areas of teenage suicide subjects. *Psychoneuroendocrinology*, *106*, 233–243. https://doi.org/10.1016/j.psyneuen.2019.04.015

Quinn, M. E., Grant, K. E., & Adam, E. K. (2017). Negative cognitive style and cortisol recovery accentuate the relationship between life stress and depressive symptoms. *Stress*, *21*(2), 119–127. https://doi.org/10.1080/10253890.2017.1414800

Stephens, M. A., Mahon, P. B., McCaul, M. E., & Wand, G. S. (2016). Hypothalamic–pituitary–adrenal axis response to acute psychosocial stress: Effects of biological sex and circulating sex hormones. *Psychoneuroendocrinology*, *66*, 47–55. https://doi.org/10.1016/j.psyneuen.2015.12.021

Sun, Y., Deng, F., Liu, Y., & Tao, F.-B. (2015). Cortisol Response to Psychosocial Stress in Chinese Early Puberty Girls: Possible Role of Depressive Symptoms. *BioMed Research International*, *2015*, 1–5. https://doi.org/10.1155/2015/781241

Thai, M., Schreiner, M. W., Mueller, B. A., Cullen, K. R., & Klimes-Dougan, B. (2021). Coordination between frontolimbic resting state connectivity and hypothalamic–pituitary–adrenal axis functioning in adolescents with and without depression. *Psychoneuroendocrinology*, *125*, 105123. https://doi.org/10.1016/j.psyneuen.2020.105123

Walther, A., Rice, T., Kufert, Y., & Ehlert, U. (2017). Neuroendocrinology of a male-specific pattern for depression linked to alcohol use disorder and suicidal behavior. *Frontiers in Psychiatry*, *7*. https://doi.org/10.3389/fpsyt.2016.00206