

# Health & Research Journal

Vol 10, No 3 (2024)

Volume 10 Issue 3 July - September 2024



Volume 10 Issue 3 July - September 2024

#### EDITORIAL

THE ROLE OF TRAINING AND SKILLS FOR THE CLINICAL TEAM (FERTILITY MIDWIVES/NURSES) IN MEDICALLY ASSISTED REPRODUCTION UNITS (M.A.R.U.)

#### RESEARCH ARTICLES

COVID-19 FEAR AND COVID-19 ANXIETY AS PREDICTORS OF EXERCISE BENEFIT-BARRIER PERCEPTION IN TYPE 2 DIABETES PATIENTS PROCESS

THE EFFECTS OF THE DARK TETRAD OF PERSONALITY BY GENDER ON ANIMAL ABUSE: A MODERATION ANALYSIS

THE EVALUATION OF THE QUALITY OF LIFE IN SURVIVORS OF CRITICAL ILLNESS AFTER DISCHARGE FROM INTENSIVE CARE UNIT: A PROSPECTIVE COHORT STUDY

DANCERS IN THE DARK: AN INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS OF THE IDENTITY PERCEPTION OF FEMALE SEX WORKERS

SUITABILITY, USABILITY AND SAFETY OF FULLY IMMERSIVE VIRTUAL REALITY APPLICATIONS FOR MOTOR AND COGNITIVE REHABILITATION IN STROKE PATIENTS: PRELIMINARY DATA

#### LETTER TO THE EDITOR

THE CASE OF "NATURE-DEFICIT DISORDER" (NDD) AND ITS COMPLICATIONS IN THE ABSENCE OF A UNIVERSALLY RELIABLE AND VALID SELF-REPORTED TOOL

#### SPECIAL ARTICLE

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Published in cooperation with the Postgraduate Program "Intensive Care Units", the Hellenic Society of Nursing Research and Education and the Helerga

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doi: [10.12681/healthresj.34200](https://doi.org/10.12681/healthresj.34200)

### To cite this article:

Ferhati, E., Thomas, G., Louka, P., & Pilafas, G. (2024). A critical discussion of the development of anxiety disorders explained by biological and psychological risk factors. *Health & Research Journal*, 10(3), 209–218. <https://doi.org/10.12681/healthresj.34200>

## SPECIAL ARTICLE

## A CRITICAL DISCUSSION OF THE DEVELOPMENT OF ANXIETY DISORDERS EXPLAINED BY BIOLOGICAL AND PSYCHOLOGICAL RISK FACTORS

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**Abstract**

The present article provides an overview of the etiology of anxiety disorders, focusing on the interplay between biological and psychological factors. Based on the global literature the prevalence of anxiety disorders affects approximately 29% of the global population. What is more, anxiety disorders can be chronic, and thus they may lead and comorbid with several mental health issues. Although genetic factors are likely to play a key role in the development of anxiety disorders, studies show that there is also an intrigued interplay between genetic and environmental factors. A specific genetic factor that has risen a great deal of attention is the serotonin-transporter-linked gene promoter region (5HTTLPR), as well as the hypothalamic-pituitary-adrenal (HPA) axis since studies discuss that the biological pathway of the stress system is also implicated in anxiety disorders. On the other hand, factors such as a stressful lifestyle and childhood maltreatment may interact negatively with genetic vulnerability to increase the risk of developing the disorders in question. For instance, parenting styles have been associated with childhood anxiety disorders in literature, including the quality of parent-child attachment, adverse and traumatic experiences. On the whole, anxiety disorders are quite complex and it is quite likely that they are influenced by a combination of biological and psychological factors. There is indeed, a clear need for further research to better understand the interplay between all factors and thus to develop effective prevention and early intervention strategies against the development of anxiety disorders.

**Keywords:** Anxiety disorders, risk factors, etiology, biopsychology, developmental psychology.**Corresponding Author:** Georgios Pilafas, **E-mail:** [giorgos.pilafas@gmail.com](mailto:giorgos.pilafas@gmail.com)

Cite as: Ferhati, E., Thomas, G., Louka, P., Pilafas, G. (2024). A critical discussion of the development of anxiety disorders explained by biological and psychological risk factors. *Health and Research Journal*, 10(3), 209-218. <https://ejournals.epublishing.ekt.gr/index.php/HealthRes/>

In our times, the most frequently occurring mental disorders are those regarding anxiety, since up to 29% of the entire population has developed some type of anxiety in their lifetime.<sup>1</sup> In anxiety disorders, the underlying cognitive structures that support stress regulation and fear responses are dysfunctional.<sup>2</sup> In general, stress is the product of a complex response system, which contains physiological, cognitive, emotional and behavioral components.<sup>3</sup> For instance, worry is a component of anxiety, which has been viewed as a cognitive process for the individual to prepare and anticipate future danger, whereas fear is a component of the response system that prepares the individual to either freeze, in order to avoid the impending punishment, or to escape as part of the 'fight or flight' response.<sup>4</sup> However, when the individual feels disproportionate levels of stress, then it becomes a mental disorder.<sup>5</sup> Thus, in anxiety disorders individuals experience constantly strong feelings of worry, vulnerability and fear, which affect their daily functioning.<sup>6,7</sup> Furthermore, these disorders usually have a chronic course and are associated with the development of other disorders, like depression.<sup>7,9</sup> Several theories have been proposed to explain the etiology and pathophysiology of the complexity of anxiety disorders<sup>10</sup> and conclude that they appear to be, like most mental health problems, an outcome of combined biological and psychological factors.<sup>5,11</sup>

Although biological vulnerability factors of anxiety disorders have received relatively little attention in causal belief research, several studies have linked genetic background to them.<sup>12</sup> More specifically, studies support the familial inheritance of these disorders due to genes,<sup>13</sup> as findings demonstrate that parents with an anxiety disorder are more likely to bequeath the same disorder to their offspring.<sup>14,15</sup> Studies of monozygotic twins (100% genetically identical) have allowed the true contribution of genetic factors to the pathogenesis or heritability of anxiety disorders to be assessed and they consistently demonstrate a modest genetic influence.<sup>16,17</sup> Even though the estimated size of twin heritability is 30-40%,<sup>13</sup> previous research, that include gene-environment interaction, indicate heritability of up to 60%.<sup>18</sup> Therefore, even if anxiety disorders are undoubtedly heritable, the current bibliography does not consistently indicate heritability as a significant or exclusive variable, since environmental factors

also play a vital role in the emergence of anxiety disorders. **Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε.**

Despite the fact that research on specific genes implicated in the development of anxiety disorders is less extensive, studies have focused on a functional polymorphism in the serotonin-transporter-linked gene promoter region (5HTTLPR).<sup>12,19,21</sup> Even so, polymorphisms in this gene have been linked to many different disorders and are unlikely to play an exclusive role in anxiety.<sup>22</sup> A meta-analysis of studies in adults proved that the short allele of the 5-HTT gene was associated with a tendency for negative emotions and anxiety.<sup>23</sup> However, research on children has produced a more mixed picture with findings showing no association between the 5-HTT gene and the anxiety predictor, the idiosyncratic style of behavioral inhibition (BI).<sup>24</sup> Moreover, while inhibition in one study was found to be associated with the long allele of the 5-HTT gene,<sup>25</sup> in another it was associated with the homozygous short allele of 5-HTT.<sup>26</sup> These puzzling results may be due to the attempt to search for simple correlations, when the relationship between gene and pathology is moderated by different factors, such as the environment.<sup>27</sup> Thus, apart from genes, which can contribute to the development of anxiety disorders, the environment also has a great influence on the individual and plays a decisive role in the manifestation of these disorders.<sup>13</sup> For example, variants in a serotonin transporter gene polymorphism are associated with anxiety sensitivity, but only in the presence of a stressful early life event, including childhood maltreatment.<sup>28</sup> This was further supported in a study on social anxiety by Fox et al.,<sup>29</sup> who found that the presence of the short 5-HTT allele remarkably increased the possibilities of shyness and behavioral inhibition in children, only when their levels of social support had been declined. This fact is explained by a theory, which states that the presence of two short alleles in the 5-HTT gene is capable of significantly increasing the individual's response to both positive and negative environmental events.<sup>30</sup> Hence, the presence of a polymorphism in the 5-HTT gene may predispose to an anxiety disorder but does not guarantee its development, for this reason the contribution of the individual's environment and early experiences is significant and should not be neglected.<sup>31</sup>

In addition to specific gene polymorphisms, the hypothalamic-

pituitary-adrenal (HPA) axis is considered the key biological pathway of the stress system, and alterations in it may be associated with genetic vulnerability.<sup>32</sup> Although it is widely proven that alterations of the HPA axis can cause psychiatric disorders, including anxiety disorders,<sup>33,34</sup> there is no clear answer as to how it is regulated.<sup>35</sup> A typical example of genetic vulnerability to anxiety is maternal anxiety disorders, which during pregnancy appear to be related to childhood anxiety disorder diagnoses.<sup>36</sup> Dysregulation of the maternal HPA axis resulting from increased levels of its end product, namely cortisol, is associated with fearful and anxious behaviors, stress reactivity as well as, negative emotional and behavioral outcomes in the infant after exposure to excessive amounts of glucocorticoids.<sup>37</sup> Nevertheless, there are some studies that evaluate the above findings as inconsistent, since they either find no relationship between cortisol levels and pregnancy-related anxiety<sup>38</sup> and general anxiety,<sup>39</sup> or they find a negative correlation with morning cortisol levels and a positive correlation with evening cortisol levels.<sup>40</sup> For instance, Pluess et al.<sup>41</sup> noticed a significant negative correlation of stress and cortisol levels in pregnant women, while Seng et al.<sup>42</sup> found lower cortisol levels in mothers with post-traumatic stress disorder (PTSD) symptoms. In line with these, evidence on the relationship between maternal anxiety disorders and cortisol levels is mixed and needs to be clarified in future research.<sup>43</sup> On the other hand, maternal stress has been proven to affect not only the HPA axis, but other biological mechanisms that later appear to create anxiety disorders in infants, such as the placental enzyme HSD11B2, which, although it protects the fetus from excessive exposure to glucocorticoids, due to high cortisol levels its function is inhibited.<sup>44</sup> Evidently, there is a complex interplay of hormonal and genetic factors, with inconsistent research results, that should be taken into account and systematically examined in order to understand the development of anxiety disorders.<sup>45</sup> While it appears that prenatal stress can create a risk for anxiety disorders, this risk and the resulting brain abnormalities can be mitigated by prenatal interventions, including cognitive behavioral therapy (CBT) and mindfulness interventions, with research showing promising results.<sup>46,47</sup>

Anxiety disorders emerge from biological factors as well as psy-

chological ones, with the individual's environment (family influences and events experienced) playing an important role in the subsequent development of the disorder.<sup>48</sup> A key question is whether the family environment is responsible for developing anxiety disorders and for that reason, studies have focused on parenting styles, particularly the two main aspects of parenting: lack of warmth/parental rejection and overcontrol.<sup>49</sup> Lack of warmth and rejection, within a cognitive context, can reinforce the child's perceptions that the world is hostile and unsupportive<sup>50</sup> while excessive control can limit a child's self-efficacy and social autonomy and can induce to an inability to cope with difficult and threatening situations.<sup>51</sup> Evidence for associations of these parenting styles with childhood anxiety disorders is mixed<sup>52</sup> but with stronger and more reliable associations for parental overcontrol.<sup>53,54</sup> More specifically, it has been shown that overcontrol is related to anxiety disorders since it reduces the child's opportunity to obtain new skills, like social skills, which leads to higher social anxiety and avoidance. **Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε.** At the other end of the spectrum, lack of warmth and parental rejection have been found to be more strongly associated with depression as children, due to rejection, acquire low self-esteem, doubt themselves and show depressive symptomatology.<sup>55</sup> Consequently, it seems that overprotection is considered as a more fundamental element in the emergence of anxiety disorders, which is also supported by theoretical models.<sup>57</sup> This is particularly relevant to social anxiety disorder (SAD) since research suggests that adults diagnosed with this disorder tend to believe that their parents were oppressive and restricted their autonomy.<sup>58,59</sup> Nonetheless, there are a few studies that disagree with the former findings, arguing that people with social anxiety remember their parents as more rejecting, critical, with lower emotional warmth and increased negativity.<sup>60,61</sup> Even though these studies have stated that parents are more negative during their interaction with their children, evidence indicates that, for the most part, negativity is less responsible for the development of anxiety disorders compared to overinvolvement.<sup>62</sup> Limited research has been conducted on parental negativity, with findings being inconclusive, since some studies found significant associations between negativity and anxiety,<sup>63</sup> while others found no relationship whatsoever.<sup>64</sup> Finally, even if these

parental characteristics, especially overcontrol, have been linked to anxiety symptomatology, some studies claim that this is only the case when accompanied by infant behavioral inhibition (BI).<sup>65</sup>

All the previous associations can be considered in the quality of parent-child attachment, which has been identified as a great factor in the occurrence of anxiety disorders.<sup>49</sup> It has been consistently argued by attachment theorists that rejecting parenting styles and reducing autonomy in a child can lead to an insecure attachment style.<sup>66</sup> For example, Moss et al. found that children classified as having disorganized attachment, two years later showed significant levels of anxiety.<sup>67</sup> Disorganized attachment, the most difficult type of insecure attachment, develops when the child's caregiver becomes a source of fear, often from some form of abuse, and results in the child's inconsistent behaviors, mistrust, and the development of many disorders, including anxiety disorders.<sup>68</sup> There are two related studies of interest, which claim that disorganized children seem to be more shy and socially anxious as they also have higher rates of social anxiety disorder.<sup>69,70</sup> Nevertheless, this correlation does not seem to have been demonstrated by other known longitudinal or prospective studies, and disorganized attachment has not always been associated with anxiety.<sup>71</sup> In fact, it is argued that disorganized children are not only less likely to develop an anxiety disorder, but this may work in reverse, and children may take control of the relationship through role reversal (i.e., taking care of their parents).<sup>72</sup> So, regardless the fact that it is not necessarily responsible for the etiology of anxiety disorders, it certainly predisposes to some type of anxiety, since children with this kind of attachment have grown up in an insecure environment, with unavailable caregivers, and therefore, perceive the behavior of others as frightening and unpredictable.<sup>72</sup> All already stated indicate that disorganized attachment might be one risk factor for the development of internalizing problems, including anxiety disorders.<sup>73</sup> Additionally, adverse and dreadful experiences (divorce, death, natural disasters, environmental changes, etc.) were closely associated with the emergence of childhood psychopathology and more markedly, with anxiety disorders.<sup>74,75</sup> In a relevant study by Goodyer et al.,<sup>76</sup> it was noticed that children experienced many negative events 12 months before they were diagnosed with an

anxiety disorder. This is further supported by Phillips et al.,<sup>77</sup> who observed that difficult situations, such as a parent's change of partner during the first 5 years of the child's life, predicted anxiety disorders in adolescence. Even if anxious children appear to have experienced multiple negative events, these findings are challenged by studies that have found reciprocal influences.<sup>49</sup> Indeed, research has shown that anxiety in childhood is associated with the occurrence of subsequent adverse events, perhaps due to worry and anxiety-related avoidance.<sup>78,79</sup> A case worth mentioning is a study by Juvonen and Graham,<sup>80</sup> who demonstrated that anxious children are more prone to be bullied at school and rejected by their peers compared to non-anxious children. From all the above results an unknown direction of the causality of anxiety disorders, which, however, seems to support that anxious children are likely to cause teasing from others due to their own behavior, just as it is equally likely that this teasing will reinforce their anxiety.<sup>27</sup>

Particular attention has been paid to specific traumatic and aversive events that have been indicated to be responsible for the pathogenesis of anxiety disorders.<sup>55</sup> Verily, numerous studies have supported that child sexual abuse is associated with high levels of anxiety disorders<sup>81,82</sup> and particularly PTSD.<sup>83</sup> Yet, sexual abuse appears to be a greater factor in the occurrence of many other forms of psychopathology, like depression.<sup>84</sup> Physical abuse was also found to be related to anxiety disorders, although relevant research is limited and findings are less consistent.<sup>85-87</sup> However, it is argued that traumatic events do not play a significant role in the development of long-term anxiety disorders, and studies examining them are mostly retrospective and lack control groups.<sup>27,88</sup> Another counterargument is that many individuals experience trauma but do not develop an anxiety disorder,<sup>89</sup> making the processes by which traumatic experiences can cause anxiety disorders complex and multifaceted.<sup>12</sup> This can be attributed to the fact that several people are genetically more vulnerable to anxiety than others, which combined with traumatic experiences, increases the chances of developing an anxiety disorder.<sup>90</sup> Indeed, research suggests that individuals exposed to harmful life experiences have altered physiological systems, such as the aforementioned HPA axis.<sup>77</sup> This was further supported by a study of abused children diagnosed with social

anxiety disorder, in which they found high cortisol levels and thus, an altered HPA axis.<sup>91</sup> Hence, adverse and stressful experiences seem to be a possible etiology of anxiety disorders, but in fact they can be influenced and manifested by the presence of certain biological factors, namely the individual/genetic vulnerability.<sup>92,93</sup>

Considering all the above, anxiety disorders are the most frequently occurring and among the most complex mental disorders, which are related to both biological and psychological factors. Biological regions, genes and alterations in physiological systems predispose the individual to an anxiety disorder but do not guarantee its development. Therefore, the environment and adverse life experiences can negatively affect anxiety levels, increasing the likelihood of the eventual manifestation of the disorder. Although these factors seem to be closely related to each other and have a significant influence on the etiology of anxiety, further research study is needed to create a clearer understanding of how they work cooperatively, which will later prove useful in prevention and early intervention for the treatment of anxiety disorders.

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