

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Risk Factors of Anxiety Disorders in Children

---

Malgorzata Dabkowska and Agnieszka Dabkowska-Mika

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/61169>

---

## Abstract

Anxiety disorders are common; lifetime prevalence for the group of disorders is estimated to be as high as 25%. The main question is What is the relative contribution of genetics and environment to etiology of anxiety disorders? The anxiety disorders are not, from a genetic perspective, etiologically homogeneous. Structural equation modeling provides estimates of variance in liability to a disorder that is attributable to additive genetic, common familial environmental, and individual-specific environmental factors. Familial aggregation that largely results from genetic risk factors has been documented for all of the major anxiety disorders. Genes predispose to two broad groups of disorders dichotomized as panic-generalized-agoraphobic anxiety versus specific phobias. The candidate genes are the ones encoding the central and peripheral nervous system receptors and transporters. Trauma in childhood disposes to further anxiety disorders through the hyperactivity of the HPA axis and the hypersecretion of CRF. Traumatic experience in developmental age leads to neurobiochemical changes in brain, typical for panic disorder or PTSD. Behavioral inhibition in early childhood is a predictor of further anxiety disorders. Some types of parental behaviors and family environment can lead to them, as well as improper interactions between parents and child.

**Keywords:** Anxiety disorders, children, risk factors, environmental, genes

---

## 1. Introduction

Anxiety disorders are among the most common psychological disorders in younger patients, affecting 6% to 20% of developed countries children and adolescents [1]. In the etiology of

---

anxiety disorders there is a complex interplay of biological and genetic vulnerabilities, temperamental qualities, negative environmental influences and negative attachment experiences, parental psychopathology, and disadvantageous sociocultural factors [2].

Biological risk factors include genetics and child temperament. Anxiety disorders are highly comorbid with each other and with mood disorders. There is a growing number of studies searching for candidate genes of anxiety disorders through human genome scan. Studies of environmental risk factors in the development of childhood anxiety disorders have focused on parent–child interactions and parental anxiety.

## **2. Environmental risk factors**

### **2.1. Gender**

Girls are more vulnerable than boys for anxiety. Female sex consistently emerges as a risk factor for the development of anxiety disorders. Females are about twice as likely as males to develop each of the anxiety disorders [3]. The female preponderance emerges early in life, and retrospective data indicate that at age 6, females are already twice as likely to have experienced an anxiety disorder as are males [4].

### **2.2. Age**

There is a typical age of onset for different kinds of anxiety disorders—separation anxiety disorder and some specific phobias usually start before age of 12 years [5]; social phobia in late childhood, adolescence, and very rarely after 25 years [5,6]. Agoraphobia, panic disorder, and general anxiety disorder usually emerge later in adolescence or early adulthood, with some cases starting even before 12 [5, 7].

### **2.3. Temperament**

The importance of emotional deregulation is emphasized in anxiety disorders. Negative emotional responses are more frequent and intensive in anxious children, as well as difficulties in reappraisal according to negative emotional situations. These children trust more on emotion regulation strategies. All of that can lead to functional impairment, intensive negative emotions, and disturbing in emotion regulation self-efficacy [8]. The vigilance–avoidance attention pattern is found in anxious adults and children, who initially gaze more at threatening pictures than nonanxious adults and children (vigilance) but subsequently gaze less at them than nonanxious adults and children (avoidance) [9]. Children and adolescents with anxiety disorders could have different temperaments and character profiles in accordance with diagnostic groups, which imply the specific pathophysiological mechanism of each anxiety disorder [10]. Behavioral inhibition in early childhood is a predictor of further anxiety disorders. Some types of parental behaviors and family environment can lead to them, as well as improper interactions between parents and child. Both parental acceptance and parental overcontrol are related to anxiety. It is confirmed that the overcontrolling behavior of parents

can be a predictor of anxiety in a child and is connected with constant fear in adolescence. What is more, an absence of maternal overcontrol can diminish the significance of high behavioral inhibition on further social anxiety symptoms. It has occurred that there is a significant connection between parents' avoiding behavior and symptoms of anxiety in child. Some studies indicate that among environmental risk factors, an inhibited temperament has the greatest impact and can moderate others' factors influence. Some results suggest that the association between behavioral inhibition and anxiety disorder is accounted for by children who have stable behavioral inhibition. Children who remained inhibited at 4, 5 1/2, and 7 1/2 years had higher rates of anxiety disorders than children who were not consistently inhibited. With few exceptions, behavioral inhibition was shown to be a risk factor for the development of anxiety disorders [11–13]. There are also indications for specificity in this association within anxiety disorders (strong associations particularly to social phobia). Toddlers and preschoolers with behavioral inhibition and a family history of anxiety disorder and stable inhibition have an increased risk of anxiety disorders, particularly social phobia, and may benefit from preventative parenting interventions. Avoidant personality disorder is reported to be especially prevalent in people with anxiety disorders. Approximately 10–50% of people who have panic disorder with agoraphobia have avoidant personality disorder, as well as about 20–40% of people who have social phobia; 45% among people with generalized anxiety disorder have avoidant personality disorder [14].

#### **2.4. Parental factors**

Infants who were anxiously attached in infancy develop more anxiety disorders during childhood and adolescence than infants who were securely attached [15]. Parents affected by anxiety disorders usually cannot learn how to manage anxiety in their children because they do not have this ability themselves. These children develop anxiety disorders more often, sometimes as early as in toddlerhood [16]. Anxiety disorders are common among offspring of anxious and depressed parents. Offspring of anxious parents were significantly more likely to have only anxiety disorders. Offspring of depressed or mixed anxious/depressed parents had a broader range of disorders and more comorbid disorders [17]. A large body of work has demonstrated that parent anxiety disorders increase the risk for similar problems in children. Parent anxiety symptoms moderated the relationship between parent- and child-externalizing symptoms, such that the strength of this relationship was reduced in the presence of high levels of parent anxiety symptoms [18]. Parental psychopathology and rearing were associated with offspring social phobia, independently as well as in their interaction. The examination the role of parental psychopathology and family environment for the risk of social phobia in a large sample of adolescents showed that parental social phobia was associated with offspring's risk to develop social phobia. Other parental anxiety disorders, depression, and alcohol use disorders were also associated with offspring social phobia. Parental rearing styles of overprotection, rejection, and lack of emotional warmth were associated with offspring social phobia. Observations suggested a continued graded relationship between familial risk factors and offspring SAD [19,20]. The risk factor of anxiety disorders during childhood is parenting behavior as a possible factor in the transmission of anxiety from parent to child. The emotions in families with an anxious parent differed significantly from families without an anxious parent [21].

Environmental mechanisms (e.g., maternal anxious attachment perceptions, maladaptive parenting practices, parental modeling of anxiety, and avoidance) may account for the observed association between parent and child anxiety [22]. The potential role of learning from parents in the development of child anxiety has three specific mechanisms: parental modeling, information transfer, and parental reinforcement of anxious/avoidant behavior. A variety of parenting practices (i.e., parental overcontrol, parental overprotection, parental emotional warmth/positivity, parental rejection/criticism, and parenting styles) could be factors that may pose risk for the development of child anxiety [23]. Both parental use of aversive control and nonresponsiveness were directly related to overall levels of child anxiety disorder-related behavior [24]. Parenting stress, parental psychopathology, and family functioning are associated with child anxiety [25,26]. Anxious attachment may lead to separation anxiety. Children with temperamental vulnerability may develop anxiety disorders, when their mastery and autonomy are restricted by overcontrolling, overprotective, and overly critical parenting styles. Parental rejection and control may lead to later anxiety and depression [27]. Anxiety disorders in children may be caused by insecure (especially anxious/resistant) attachment relationships with caregivers [27, 15]. Different attachment patterns (secure, ambivalent, avoidant, and disorganized) may relate to different types of anxiety symptoms and that behavioral inhibition may moderate these relations.

## **2.5. Culture factors**

The culture-specific expression of anxiety is a risk factor for anxiety disorders, for example, Asian cultures typically show the lowest rates, whereas Russian and US samples show the highest rates of social anxiety disorder. The prevalence and expression of social anxiety depends on the particular culture. Social anxiety is assumed to be related to cultural norms across countries. In some works, researchers compared individualistic and collectivistic countries and found higher social anxiety and more positive attitudes toward socially avoidant behaviors in collectivistic rather than in individualistic countries [28–30].

## **2.6. Toxic environment**

Patients with environmental illness experience a large number of psychiatric symptoms. Anxiety disorders were significantly more frequent in patients with environmental illness [31]. Organic brain damage with cognitive and behavioral impairment can be caused by acute and toxic exposure. Even low-to-moderate exposure, when it is chronic, may lead to anxiety and mood disturbances. Lead exposure particularly can result in anxiety and depression [32, 33].

## **2.7. A unique environmental factor and common shared environmental factor**

It is said that two groups of disorders (specific phobias versus generalized/panic anxiety and agoraphobia, with social phobia between them) are associated with two genetic factors. Common and (in a greater degree) unique environmental factors shared across the disorders can explain remaining associations between the disorders. In the results of analyses from more than 5000 members of male–male and female–female twin pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders, it occurred that shared environmental

influences do not play a major role, as a single common factor was calculated below 12% of the total variance for any disorder. Researchers describe unique environmental factors as single common factor plus effects, which are characteristic for a disease [34]. During a lifetime, life experiences (unique for the patient or shared with other family members) may further influence the risk for anxiety disorders. It would have different significance, depending on the disorder. Something called a “set of unique environmental factors” can lead to one or another anxiety disorder [34].

## **2.8. Life experience/childhood adversities**

The experience of a traumatic event may influence the development of anxiety disorders. Trauma in childhood disposes to further anxiety disorders through the hyperactivity of the HPA axis and the hypersecretion of CRF. Traumatic experience in developmental age leads to neurobiochemical changes in brain, typical for panic disorder or PTSD. Because of early trauma, there is change of genes and increase in anxiety sensitivity.

Experience of childhood trauma (e.g., sexual abuse) increases the risk of psychiatric or substance use disorder in maturity. Exposure of children to early adverse experiences is a risk factor for developing anxiety disorders. Early life stress, causing the chronic sensitization of those central nervous system circuits, which regulate stress and emotion, may be a biological explanation of increased vulnerability to stress and further development of anxiety. Childhood maltreatment has been linked to a variety of changes in brain structure and function and stress-responsive neurobiological systems. Deprivation of developmentally appropriate experience may reduce neuronal activity, resulting in a generalized decrease in neurotrophin production, synaptic connectivity, and neuronal survival, resulting in profound abnormalities in brain organization and structure [35]. Thus, childhood abuse and exposure to domestic violence can lead to numerous differences in the structure and physiology of the brain that expectedly would affect multiple human functions and behaviors [36, 37]. Neurobiological evidence supports the hypothesis of dysfunction in hippocampus, amygdala, medial prefrontal cortex, and other limbic structures believed to mediate anxiety and mood dysregulation following early abuse [37]. There are similarities in neurobiological results between some studies on early life stress in children and in animals. For example, children who suffer from generalized anxiety disorders and anticipated a laboratory stress task had increased levels of ACTH and normal levels of cortisol [38]. Altered behavioral and hormonal responses to central noradrenergic stimulation have been observed in children with several anxiety disorders. Neurobiological alterations are also present in children with PTSD related to early trauma. It may be that early life stress affects neurobiological function in children with other anxiety disorders as well, similar to findings in early-onset depression [39]. The adverse childhood experiences including abuse, witnessing domestic violence, and serious household dysfunction had a strong, graded relationship to the prevalence and risk of affective disturbances. For children with more than four experiences, the risk of panic reactions and anxiety was increased 2.5- and 2.4 -fold, respectively [40]. There is an etiological relation between stressful life events (unique to the individual or common to other members of the family) and anxiety disorders. Its effects on disorders are probably nonspecific, as many kinds of childhood adversity (loss events—

e.g., parental divorce; parental psychopathologies—e.g., maternal depression; interpersonal traumas—e.g., rape and natural disaster) are associated with adult psychiatric outcomes with little specificity, including anxiety disorders [41, 42]. These adversities were consistently associated with onset, but not persistence, of anxiety disorders [41].

### **2.9. Parental loss**

Childhood parental loss or separation has been linked to various forms of adult psychopathologic characteristic [43, 44]. The study evaluating the relationship between parental loss prior to age 17 years and adult psychopathology in 1018 pairs of female twins from a population-based registry has shown the impact of parent death or separation for the risk of anxiety disorders. Researchers found association between parental separation (but not parental death) and increased risk for generalized anxiety disorders. Parental death and separation from mother (but not father) were related to panic disorder. A higher probability of developing phobia due to parental death (but no parental separation) was described. A model that includes parental loss as a form of specified family environment shows if it is truly an environmental risk factor for adult psychopathologic conditions [44]. Not only loss of parent has a relationship with affective disorders but also lack of adequate parental care takes important role in the increased risk of psychiatric disorders in adulthood. Studies on caregiving arrangements indicate that lack of care (characterized as neglecting rather than adverse behavior of parent) is associated with higher risk of depression. It is loss of mother rather than father that has impact more frequent [45].

### **2.10. Sexual abuse**

Childhood sexual abuse is a strong risk factor of anxiety disorders. A study about the consequences of childhood sexual abuse in a birth cohort of more than 1,000 New Zealand children studied at the age of 18 years showed that children reporting sexual abuse had higher rates of anxiety disorder than those not reporting. The findings suggest that sexual abuse, particularly severe childhood sexual abuse, was associated with increased risk of psychiatric disorder in young adults even when due allowance was made for prospectively measured confounding factors [46]. Childhood sexual abuse has been found to elevate the risk for adult GAD and panic disorder, as well as other psychiatric and substance use disorders [46, 47]. Studies of the impact of traumatic events on health have shown that the history of childhood sexual or physical abuse was significantly more frequent in patients with panic disorder than those with social phobia. Rates of abuse of patients with generalized anxiety disorder were between results of these other groups, without significant differences [42]. Women with childhood sexual abuse have a substantially increased risk for developing a wide range of psychopathology. Most of this association is due to more severe forms of sexual abuse. The significant ORs for GAD and panic disorder were all approximately 1.9 [47]. In a group of 1411 women who report childhood sexual abuse (three levels: nongenital, genital, and intercourse), association with psychiatric disorders was assessed. Self-reported childhood sexual abuse was positively associated with all disorders, the most with genital and especially intercourse sexual abuse.

### **2.11. Peer violence**

Bullying behavior is a frequent risk factor of anxiety disorder among adolescents. Twenty-percent of victims scored within the clinical range on a standard depression and anxiety measure [48].

Peer victimization was positively related to child-reported anxiety, social physique anxiety, and loneliness [49]. Bullying experiences are connected not only to concurrent psychiatric symptoms but also to future psychiatric symptoms, especially anxiety disorders [50, 51].

Bullying should be seen as an indicator of risk of various mental disorders in adolescence. Finnish adolescents taking part in the School Health Promotion Study were surveyed about bullying and victimization in relation to several psychiatric disorders. Anxiety was most frequent among bully victims and equally common among bullies and victims [52]. The relationship among bullying, victimization, and anxiety may be connected with sex. Sex differences were noted on measures of peer victimization and anxiety with boys reporting more victimization but less anxiety than girls [53].

### **2.12. Economical factors**

Most children with anxiety disorders are from middle- to upper-middle class families; however, 50–75% of those with separation anxiety disorder come from low socioeconomic status homes [54–56]. Rates of anxiety disorders are greater for those with socioeconomic status disadvantage [57]. Socioeconomic status is one of many possible antecedents in the development of social anxiety disorder [58].

## **3. Genetic factors**

Genetic factors play a significant role in etiology of anxiety disorders; for example, inherited risk factor for social phobia is estimated as 47% [59].

Increased risk for anxiety disorder in children occurs if at least one parent has anxiety disorder [60], or if both parents are affected [61, 62]. Common genetic risk factors for major depression and anxiety disorder have been described as “bidirectional”; both parental major depression increased the risk of anxiety disorder in child [63, 64], and parental anxiety disorder increased risk of depression in child [62, 65].

### **3.1. Twin studies**

Torgersen [66] found that anxiety disorders (in total) are two times more frequent in MZ than in DZ co-twins; GAD is two times more frequent in MZ than in DZ co-twins. In a group with panic disorders and agoraphobia with panic attacks, anxiety disorders with panic attacks were even more than five times as frequent in MZ as in DZ.

There was research on 1030 pairs of twins about interrelationship between genetic and environmental risk factors for pairs of anxiety disorders and other mental diseases. The

researchers found that anxiety disorders are genetically heterogeneous. However, there is one common genetic risk factor (with great impact) for phobia, panic disorder, and bulimia nervosa and another factor for major depression and generalized anxiety disorder [67].

A cohort study on 1412 pairs of MZ and DZ twins, ages 8–16 years [68], suggested that genetic influences on anxiety in childhood differ according to sex (greater extent in girls than in boys). Additive genetic effects play a moderate role in the etiology of manifest anxiety among females, but a more modest role for males. Moderate additive genetic effects were reported in another study on adult patients with generalized anxiety [69].

A significant familial aggregation according to panic disorder, GAD, and phobias was shown in meta-analysis based on family and twin studies [70].

Quite often, there is a comorbidity of anxiety disorder and another anxiety disorder or mood disorder [71]. It is consistent with the results indicating the same genetic factors for GAD and major depression [72, 73].

It is shown that polymorphism in the serotonin transporter gene regulatory region is associated with anxiety-related traits (3–4% of total variation and 7–9% of inherited variance in patients and their sibships) [74].

Through human scan genome, chromosomes 1, 7, 9, and 11 were linked to panic attacks and chromosome 3 to agoraphobia [75–77]. Analysis of links exhibits loci for panic attacks on chromosome 9q [77].

There is a growing number of studies about the significant role of FK506-binding protein 51 (FKBP5), a co-chaperone of steroid hormone receptors. It regulates stress-induced GR-mediated effects. Polymorphism in this gene is related with GR sensitivity and can regulate stress hormone system. Specific alleles of FKBP5 are associated with major depression, bipolar disorder, and posttraumatic stress disorder, as well as with faster response to antidepressant treatment [78]. It can lead to increased risk of stress-related psychiatric disorders when its genetic variation interacts with early life stress (ELS) to epigenetically program GR-induced transcription of FKBP5 [79].

Demethylation of allele-specific FKBP5 DNA interacts between childhood trauma and gene transcription, leading to dysfunction of the stress hormone system, immune cells, and those brain areas, which are associated with stress regulation [80].

#### 4. Summary

An anxiety disorder during adolescence confers a strong risk for recurrent anxiety disorders during early adulthood [81]. In the future, adolescents with anxiety disorders are at an increased risk of subsequent anxiety, depression, illicit drug dependence, and educational underachievement as young adults.

Clinical features of anxiety (e.g., higher severity, duration, and avoidance) as well as comorbid other mental disorders are particularly useful for predicting an unfavorable course of anxiety

disorders [82]. Early psychoeducation program for parents could decrease risk for anxiety disorder. As environmental risk factors are already well known, the next step is to distinguish what predictors have the greatest impact and how to moderate them. Vantage sensitivity hypothesis said that some genetic variants moderate outcome of positive intervention [83]. Through studies on trajectories of behaviorally inhibited children, it occurred that some inhibited infants and toddlers develop into normal children [84].

Knowledge of risk factors enables preventive actions with respect to the developing anxiety disorders in children. It seems important to undertake actions to increase the resilience capacity of individuals to cope with traumatic events. Donovan and Spence [85] present the results of research regarding the prevention of anxiety disorders. The main protective factors are social support in the presence of traumatic experiences and coping skills in the resilience to anxiety. Methods of prevention of childhood anxiety disorders could be divided to child, parent, and environment strategies.

## Author details

Malgorzata Dabkowska<sup>1\*</sup> and Agnieszka Dabkowska-Mika<sup>2\*</sup>

\*Address all correspondence to: [gosiadab@interia.pl](mailto:gosiadab@interia.pl) [doagnieszki@interia.pl](mailto:doagnieszki@interia.pl)

1 Collegium Medicum, Nicolaus Copernicus University, Torun, Bydgoszcz, Poland

2 Psychiatry Clinic, Clinical Hospital of K. Jonscher, Poznan, Poland

## References

- [1] Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, Ginsburg GS, Rynn MA, McCracken J, Waslick B, Iyengar S, March JS, Kendall PC. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *New England Journal of Medicine*. 2008; 359,26:2753–2766. DOI: 10.1056/NEJMoa0804633.
- [2] Pine DS, Grun J. Childhood anxiety: integrating developmental psychopathology and affective neuroscience. *Journal of Child and Adolescent Psychopharmacology*. 1999;9,1:1–12. DOI: 10.1089/cap.1999.9.1.
- [3] Costello EJ, Mustillo S, Erkanli A, et al. Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*. 2003;60:837–844. DOI:10.1001/archpsyc.1996.01830110071009.
- [4] Lewinsohn PM, Gotlib IH, Lewinsohn M, Seeley JR, Allen NB. Gender differences in anxiety disorders and anxiety symptoms in adolescents. *Journal of Abnormal Psychology*. 1998;107, 1:109–117. DOI.org/10.1037/0021-843X.107.1.109.

- [5] Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*. 2005; 62:593–602. DOI: 10.1001/archpsyc.62.6.593.
- [6] Wittchen HU, Fehm L. Epidemiology and natural course of social fears and social phobia. *Acta Psychiatrica Scandinavica*. 2003; 108(Suppl 417):4–18. DOI: 10.1034/j.1600-0447.108.s417.1.x.
- [7] Wittchen HU, Nocon A, Beesdo K, et al. Agoraphobia and panic: prospective-longitudinal relations suggest a rethinking of diagnostic concepts. *Psychotherapy and Psychosomatics*. 2008; 77:147–157. DOI: 10.1159/000116608.
- [8] Carthy T, Horesh N, Apter A, Gross JJ. Patterns of emotional reactivity and regulation in children with anxiety disorders. *Journal of Psychopathology and Behavioral Assessment*. 2010;32,1(March 2010b):23–36. DOI: 10.1007/s10862-009-9167-8.
- [9] In-Albon T, Kossowsky J, Schneider S. Vigilance and avoidance of threat in the eye movements of children with separation anxiety disorder. *Journal of Abnormal Child Psychology*. 2010;38,2:225–235. DOI:10.1007/s10802-009-9359-4.
- [10] Soo-churl C, Sun-woo J, Boong-nyun K, Jun-won H, Min-sup S, Jae-won K, Dong-seon C, Hyo-won K. Temperament and character among Korean children and adolescents with anxiety disorders. *European Child and Adolescent Psychiatry*. 2009; 18:60–64. DOI: 10.1007/s00787-008-0699-3.
- [11] Caspi A, Moffitt TE, Newman DL, et al. Behavioral observations at age 3 years predict adult psychiatric disorders. *Archives of General Psychiatry*. 1996;53:1033–1039.
- [12] Hayward C, Killen JD, Kraemer HC, et al. Linking self-reported childhood behavioral inhibition to adolescent social phobia. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1998;37:1308–1316. DOI: 10.1097/00004583-199812000-00015.
- [13] Biederman J, Hirshfeld-Becker DR, Rosenbaum JF, et al. Further evidence of association between behavioral inhibition and social anxiety in children. *American Journal of Psychiatry*. 2001;158,10:1673–1679. DOI:10.1176/appi.ajp.158.10.1673.
- [14] Van Velzen CJM. *Social Phobia and Personality Disorders: Comorbidity and Treatment Issues*. Groningen: University Library Groningen. 2002. Available from: <http://irs.ub.rug.nl/ppn/240921941>.
- [15] Warren SL, Huston L, Egeland B, Sroufe LA. Child and adolescent anxiety disorders and early attachment. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36,5:637–644.
- [16] Hirshfeld-Becker DR, Biederman J. Rationale and principles for early intervention with young children at risk for anxiety disorders. *Clinical Child and Family Psychology Review*. 2002;5,3:161–172. DOI:10.1023/A:1019687531040.

- [17] Beidel DC, Turner SM. At risk for anxiety: I. Psychopathology in the offspring of anxious parents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36,7:918–924. DOI 10.1097/00004583-199707000-00013.
- [18] Burstein M, Ginsburg GS, Jenn-Yun Tein JY. Parental anxiety and child symptomatology: an examination of and interactive effects of parent psychopathology. *Journal of Abnormal Child Psychology*. 2010;38,7:897–909. DOI: 10.1007/s10802-010-9415-0.
- [19] Knappe S, Beesdo K, Fehm L, Lieb R, Wittchen HU. Associations of familial risk factors with social fears and social phobia: evidence for the continuum hypothesis in social anxiety disorder? *Journal of Neural Transmission*. 2000a;1166:639–648. DOI: 10.1007/s00702-008-0118-4.
- [20] Knappe S, Lieb R, Beesdo K, Fehm L, Low NC, Gloster AT, Wittchen HU. The role of parental psychopathology and family environment for social phobia in the first three decades of life. *Depression and Anxiety*. 2009b;26,4:363–370. DOI: 10.1002/da.20527.
- [21] Turner SM, Beidel DC, Roberson-Nay R, Tervo K. Parenting behaviors in parents with anxiety disorders. *Behaviour Research and Therapy*. 2003; 41,5:541–554. DOI: [http://dx.doi.org/10.1016/S0005-7967\(02\)00028-1](http://dx.doi.org/10.1016/S0005-7967(02)00028-1).
- [22] Fisak B, Grills-Taquechel. Parental modeling, reinforcement, and information transfer: risk factors in the development of child anxiety? *Clinical Child and Family Psychology*. 2007;10:213–231. DOI:10.1007/s10567-007-0020-x.
- [23] Ginsburg GS, Schlossberg MC. Family-based treatment of childhood anxiety disorders. *International Review of Psychiatry*. 2002;14:143–154. DOI: 10.1080/09540260220132662.
- [24] Mellon RC, Moutavelis AG. Parental educational practices in relation to children's anxiety disorder-related behavior. *Journal of Anxiety Disorders*. 2011;25,6:829–834.
- [25] Victor AM, Bernat DH, Bernstein GA, Layne AE. Effects of parent and family characteristics on treatment outcome of anxious children. *Journal of Anxiety Disorders*. 2007; 21,6:835–848. DOI: 10.1016/j.janxdis.2006.11.005.
- [26] Manassis K, Hood J. Individual and familial predictors of impairment in childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1998;37:428–434. DOI: 10.1097/00004583-199804000-00021. Rapee RM. Potential role of childrearing practices in the development of anxiety and depression. *Clinical Psychology Review*. 1997;17,1:47–67. DOI: 10.1016/S0272-7358(96)00040-2.
- [27] Rapee RM. Potential role of childrearing practices in the development of anxiety and depression. *Clinical Psychology Review*. 1997;17,1:47–67. DOI: 10.1016/S0272-7358(96)00040-2.
- [28] Hofmann SG, Anu Asnaani MA, Hinton D. Cultural aspects in social anxiety and social anxiety disorder. *Depression and Anxiety*. 2010;27,12:1117–1127. DOI: 10.1002/da.20759.

- [29] Hong JJ, Woody SR. Cultural mediators of self-reported social anxiety. *Behaviour Research and Therapy*. 2007;45,8:1779–1789. DOI: 10.1016/j.brat.2007.01.011.
- [30] Heinrichs N, Rapee RM, Alden LA, Bogels S, Hofman SG, Oh KJ, et al. Cultural differences in perceived social norms and social anxiety. *Behaviour Research and Therapy*. 2006;44:1187–1197. DOI: 10.1016/j.brat.2005.09.006.
- [31] Bornschein S, Hausteiner C, Konrad F, Förstl H, Zilker T. Psychiatric morbidity and toxic burden in patients with environmental illness: a controlled study. *Psychosomatic Medicine*. 2006;68,1:104–109. DOI: 10.1097/01.psy.0000195723.38991.bf.
- [32] Morrow LA, Gibson C, Bagovich GR, Stein L, Condray R, Scott A. Increased incidence of anxiety and depressive disorders in persons with organic solvent exposure. *Psychosomatic Medicine*. 2000;62,6:746–750. DOI: 10.1097/00006842-200011000-00002.
- [33] Morrow LA, Stein L, Bagovich GR, Condray R, Scott A. Neuropsychological assessment, depression, and past exposure to organic solvents. *Applied Neuropsychology*. 2001; 2:65–73. DOI: 10.1207/S15324826AN0802\_1.
- [34] Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Archives of General Psychiatry*. 2005;62,2:182–189. DOI:10.1001/archpsyc.62.2.182.
- [35] Perry BD. Childhood experience and the expression of genetic potential: what childhood neglect tells us about nature and nurture. *Brain and Mind*. 2002;3:79–100. DOI: 10.1023/A:1016557824657.
- [36] Teicher MH. Wounds that time wouldn't heal: the neurobiology of childhood abuse. *Cerebrum*. 2000; 2:50–67. www.dana.org.
- [37] Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP. Developmental neurobiology of childhood stress and trauma. *Psychiatric Clinics of North America*. 2002; 25:397–426. DOI: 10.1016/S0193-953X(01)00003-X.
- [38] Gerra G, Zaimovic A, Zambelli U, Timpano M, Reali N, Bernasconi S, et al. Neuroendocrine responses to psychological stress in adolescents with anxiety disorder. *Neuropsychobiology*. 2000; 42:82–92. DOI:10.1159/000026677.
- [39] Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry*. 2001;49,12:1023–1039. DOI: 10.1016/S0006-3223(01)01157-X.
- [40] Anda RA, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience*. 2006;256,3:174–186. DOI:10.1007/s00406-005-0624-4.

- [41] Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychological Medicine*. 1997;27:1101–1119. DOI: <http://dx.doi.org/10.1017/S0033291797005588>.
- [42] Safren SA, Gershuny BS, Marzol P, Otto MW, Pollack MH. History of childhood abuse in panic disorder, social phobia, and generalized anxiety disorder. *Journal of Nervous and Mental Disease*. 2002; 190:453–456. DOI: [10.1097/00005053-200207000-00005](http://dx.doi.org/10.1097/00005053-200207000-00005).
- [43] Lindesay J. Phobic disorders in the elderly. *British Journal of Psychiatry*. 1991;159:531–541. DOI: [10.1192/bjp.159.4.531](http://dx.doi.org/10.1192/bjp.159.4.531).
- [44] Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Childhood parental loss and adult psychopathology in women: a twin study perspective. *Behaviour Research and Therapy*. 1992;49:109–116. DOI: [10.1001/archpsyc.1992.01820020029004](http://dx.doi.org/10.1001/archpsyc.1992.01820020029004).
- [45] Harris T, Brown GW, Bifulco A. Loss of parent in childhood and adult psychiatric disorder: the role of lack of adequate parental care. *Psychological Medicine*. 1986;16:641–659. DOI: <http://dx.doi.org/10.1017/S0033291700010394>.
- [46] Fergusson DM, Horwood LJ, Lynskey MT. Childhood sexual abuse and psychiatric disorder in young adulthood, II: psychiatric outcomes of childhood sexual abuse. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996; 35:1365–1374. DOI: [10.1097/00004583-199610000-00024](http://dx.doi.org/10.1097/00004583-199610000-00024).
- [47] Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. *Archives of General Psychiatry*. 2000;57:953–959. DOI: [10.1001/archpsyc.57.10.953](http://dx.doi.org/10.1001/archpsyc.57.10.953).
- [48] Espelage DL, Holt MK. Bullying and victimization during early adolescence. Peer influences and psychosocial correlates. *Journal of Emotional Abuse*. 2001;2,2–3:123–142. DOI: [10.1300/J135v02n02\\_08](http://dx.doi.org/10.1300/J135v02n02_08).
- [49] Storch EA, Milsom VA, DeBraganza N, Lewin AB, Geffken GR, Silverstein JH. Peer victimization, psychosocial adjustment, and physical activity in overweight and at-risk-for-overweight youth. *Journal of Pediatric Psychology*. 2007; 32,1:80–89. DOI: [10.1093/jpepsy/jsj113](http://dx.doi.org/10.1093/jpepsy/jsj113).
- [50] Kumpulainen K., Räsänen E. Children involved in bullying at elementary school age: their psychiatric symptoms and deviance in adolescence: an epidemiological sample. *Child Abuse & Neglect*. 2000;24,12:1567–1577. DOI: [10.1016/S0145-2134\(00\)00210-6](http://dx.doi.org/10.1016/S0145-2134(00)00210-6).
- [51] Craig WM. The relationship among bullying, victimization, depression, anxiety, and aggression in elementary school children. *Personality and Individual Differences*. 1998;24,1:123–130. DOI: [10.1016/S0191-8869\(97\)00145-1](http://dx.doi.org/10.1016/S0191-8869(97)00145-1).

- [52] Kaltiala-Heino RA, RIMPELÄ M, Rantanen P, Rimpela A. Bullying at school—an indicator of adolescents at risk for mental disorders. *Journal of Adolescence*. 2000;23,6:661–674. DOI: 10.1006/jado.2000.0351.
- [53] Grills AE, Ollendick TH. Peer victimization, global self-worth, and anxiety in middle school children. *Journal of Clinical Child & Adolescent Psychology*. 2002;31,1:59–68. DOI:10.1207/S15374424JCCP3101\_08.
- [54] Last CG, Francis G, Hersen M, et al. Separation anxiety and school phobia: a comparison using DSM III criteria. *American Journal of Psychiatry*. 1987;144,5:653–657. DOI.org/10.1176/ajp.144.5.653.
- [55] Last CG, Perrin S, Hersen M, et al. DSM-III-R anxiety disorders in children: sociodemographic and clinical characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1992; 31,6:1070–1076. DOI: 10.1097/00004583-199211000-00012.
- [56] Velez CN, Johnson J, Cohen P. A longitudinal analysis of selected risk factors for childhood psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1989; 28,6:861–864. DOI: 10.1097/00004583-198911000-00009.
- [57] Merikangas KR. Vulnerability factors for anxiety disorders in children and adolescents. *Child and Adolescent Psychiatric Clinics of North America*. 2005;14,4:649–679. DOI: 10.1016/j.chc.2005.06.005.
- [58] Brook ChA, Schmidt LA. Social anxiety disorder: a review of environmental risk factors. *Neuropsychiatric Disease Treatment*. 2008;4,1:123–143. DOI: <http://dx.doi.org/10.2147/NDT.S1799>
- [59] Skre I, Onstad S, Torgersen S, Philos DR, Lygren S, Kringlen E. The heritability of common phobic fear: a twin study of a clinical sample. *Journal of Anxiety Disorders*. 2000; 14 (6):549–562.
- [60] Wittchen HU, Kessler RC, Pfister H, Lieb M. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatrica Scandinavica. Supplementum*. 2000; 406:14–23. DOI: 10.1111/j.0065-1591.2000.acp29-03.x
- [61] Merikangas KR, Avenevoli S, Dierker L, Grillon C. Vulnerability factors among children at risk for anxiety disorders. *Biological Psychiatry*. 1999 Dec 1;46(11):1523–1535. DOI: 10.1016/S0006-3223(99)00172-9.
- [62] Johnson JG, Cohen P, Kasen S, Brook JS. Parental concordance and offspring risk for anxiety, conduct, depressive, and substance use disorders. *Psychopathology*. 2008; 41(2):124–128. DOI: 10.1159/000112028.
- [63] Lieb R, Isensee B, Höfler M, Pfister H, Wittchen HU. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitu-

- dinal community study. *Archives of General Psychiatry*. 2002 Apr;59(4):365–374. DOI: 10.1001/archpsyc.59.4.365.
- [64] Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. Offspring of depressed parents: 20 years later. *American Journal of Psychiatry*. 2006 Jun; 163(6):1001–1008. DOI: 10.1176/appi.ajp.163.6.1001.
- [65] Kendler KS, Davis CG, Kessler RC. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *British Journal of Psychiatry*. 1997; 170(June 1997):541–548. DOI: 10.1192/bjp.170.6.541.
- [66] Torgersen S. Genetic factors in anxiety disorders. *Archives of General Psychiatry*. 1983;40(10):1085–1089. DOI: 10.1001/archpsyc.1983.01790090047007.
- [67] Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry*. 1995;52(5):374–383. DOI: 10.1001/archpsyc.1995.03950170048007.
- [68] Topolski TD, Hewitt JK, Eaves LJ, Silberg JL, Meyer JM, Rutter M, Pickles A, Simonoff E. Genetic and environmental influences on child reports of manifest anxiety and symptoms of separation anxiety and overanxious disorders: a community based twin study. *Behavior Genetics*. 1997 Jan;27(1):15–28. DOI: 10.1023/A:1025607107566.
- [69] Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and generalized anxiety disorder: same genes, (partly) different environments? *Archives of General Psychiatry*. 1992;49(9):716–722. DOI:10.1001/archpsyc.1992.
- [70] Hetttema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry*. 2001; 158:1568–1578. DOI: 10.1176/appi.ajp.158.10.1568.
- [71] Maser JD, Cloninger CR (eds.). *Comorbidity of Mood and Anxiety Disorders*. Washington, DC, American Psychiatric Press, 1990.
- [72] Roy MA, Neale MC, Pedersen NL, Mathé AA, Kendler KS. A twin study of generalized anxiety disorder and major depression. *Psychological Medicine*. 1995 Sep;25(5): 1037–1049. DOI: <http://dx.doi.org/10.1017/S0033291700037533>.
- [73] Kendler KS. Major depression and generalised anxiety disorder. Same genes, (partly) different environments—revisited. *British Journal of Psychiatry*. Supplement. 1996 Jun;(30):68–75.
- [74] Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996 Nov 29;274(5292): 1527–1531. DOI: 10.1126/science.274.5292.1527.

- [75] Gelernter J, Bonvicini K, Page G, Woods SW, Goddard AW, Kruger S, Pauls DL, Goodson S. Linkage genome scan for loci predisposing to panic disorder or agoraphobia. *Am J Med Genet* 2001; 105 (6):548–557. DOI: 10.1002/ajmg.1496.
- [76] Crowe RR, Goedken R, Samuelson S, Wilson R, Nelson J, Noyes R Jr. Genomewide survey of panic disorder. *American Journal of Medicinal Genetics*. 2001; 105 (I):105–109. DOI: 10.1002/1096-8628(20010108).
- [77] Thorgerisson TE, Oskarsson H, Desnica N, Kostic JP, Stefansson JG, Kolbeinsson H, Lindal E, Gagunashvili N, Frigge ML, Kong A, Stefansson K, Gulcher JR. Anxiety with panic disorder linked to chromosome 9q in Iceland. *American Journal of Human Genetics*. 2003; 72 (5):1221–1230. DOI: 10.1086/375141.
- [78] Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology*. 2009 Dec;34(Suppl 1):S186–S195. DOI: 10.1016/j.psyneuen.2009.05.021.
- [79] Klengel T, Binder EB. Gene-environment interactions in major depressive disorder. *Canadian Journal of Psychiatry*. 2013 Feb;58(2):76–83.
- [80] Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holsboer F, Heim CM, Ressler KJ, Rein T, Binder EB. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nature Neuroscience*. 2013 Jan;16(1):33–41. DOI: 10.1038/nn.3275.
- [81] Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders, *archives of general psychiatry*. 1998;55,1:56–64. DOI: 10.1001/archpsyc.55.1.56.
- [82] Asselmann E, Katja Beesdo-Baum K. Predictors of the course of anxiety disorders in adolescents and young. *Current Psychiatry Reports*. 2015;17:7. DOI: 10.1007/s11920-014-0543-z.
- [83] Pluess M, Belsky J. Vantage sensitivity: individual differences in response to positive experiences. *Psychological Bulletin*. 2013; 139,4:901–916. DOI: 10.1037/a0030196.
- [84] Degnan KA, Fox NA. Behavioural inhibition and anxiety disorders: multiple levels of a resilience process. *Development and Psychopathology*. 2007; 19:729–746. DOI: 10.1017/S0954579407000363.
- [85] Donovan CL, Spence SH. Prevention of childhood anxiety disorders. *Clinical Psychology Review*. 2000; 20:509–531. DOI:10.1016/S0272-7358(99)00040-9.