



## Psychosomatic Aspects of The Development of Comorbid Pathology: A Review

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### Abstract

**Background:** The article reviews the literature data on various somatic and mental pathologies, which are comorbid processes with similar pathophysiological, genetic and neurochemical mechanisms. The psychosomatic manifestations of cardiovascular diseases and coronavirus disease (COVID-19) are considered. Particular attention is paid to post-traumatic stress disorder of participants in local wars. Comorbid pathology, in combination with depression and anxiety, aggravates the course of the disease, leading to disability in the adult population and premature death.

**Methods:** The literature was searched in PubMed, Mendeley, Google Scholar, and ScienceDirect databases to identify relevant studies published from 2012 to 2022.

**Results:** Our literature search revealed a bidirectional association between comorbid psychiatric and somatic disorders. The prevalence of somatic diseases increases in people with a predominance of mental disorders.

**Conclusion:** There is growing evidence that the combination of anxiety-depressive disorders and physical illness worsens the severity of the disease, complicating the diagnosis of the presence of one and/or several physical symptoms. However, more clinical trials are still needed to determine their full mechanisms of action.

**Keywords:** Comorbid Pathology, Depression, Anxiety, Stress, COVID-19, Post-traumatic Stress Disorder (PTSD), Cardiovascular Disease (CVD)

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### Introduction

In recent decades, the increasing frequency of technogenic and environmental disasters, infectious diseases, social cataclysms, and local wars have led to an increase in the prevalence of psychosomatic diseases in society. These psychogenic events can lead to a violation of mental and physical health and social adaptation of a person in soci-

ety. Mental illness is increasingly recognized as a global health priority and, given its economic burden, is one of the development priorities (1). In 2019, 1 out of every 8 people, or 970 million people worldwide, suffered from a mental disorder, the most common of which were anxiety and depressive disorders (2). As of 2020, the number of

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#### ↑What is "already known" in this topic:

Psychosomatic disorders in many comorbid diseases have similar development mechanisms, manifesting themselves as depressive and anxiety states, which significantly change the clinical picture and the course of the main nosology, as the nature and the severity of complications.

#### →What this article adds:

In this review article, mental manifestations were comorbid in individuals with completely different somatic pathologies, and specialists need to know the neurobiological and genetic mechanisms of the development of a psychosomatic disorder for diagnostic tools and targeted treatment.

people living with anxiety and depressive disorders has increased significantly due to the COVID-19 pandemic. The combination of mental disorders and somatic diseases makes it difficult to diagnose and carry out psycho-corrective and rehabilitation measures and also worsens the course of the disease.

Currently, the World Health Organization (WHO) considers depression not only as a psychiatric problem but also as an important general medical problem, which is determined by its high prevalence in the population, its association with a number of somatic disorders, and its leading cause of disability worldwide, affecting at least 350 million people (3). In medical practice, there are often patients with comorbid depression associated with worsening mental and clinical outcomes (4, 5).

Comorbidity is characterized by the simultaneous coexistence of two or more diseases that independently follow their usual trajectories (6). On the other hand, comorbid pathology aggravates the course of the disease, manifested by attacks of deep depression combined with anxiety, disability of the adult population, and ultimately, premature death. Comorbid diseases are caused by an increased risk of severe death in humans or a massive non-communicable disease (7, 8). Psychosomatic diseases are called diseases that occur against the background of psycho-emotional stress after traumatic events, the result of which affects the physiological functioning of the individual's body. The Diagnostic and Statistical Manual of Mental Disorders - 5th edition (DSM-5) refers to this condition as somatic symptom disorder (SSD), which includes somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder (9).

The etiology of psychosomatic disorders is multifactorial. A number of factors, such as personality traits, genetic, environmental and biological factors, play an important role in the pathogenesis of psychosomatic disorders (10). Over the last quarter of a century, there has been a sharp increase in psychogenic disorders, in general, from 38 to 42% among patients who consulted doctors. There is evidence that psychological (emotional) factors are associated with more than 40 types of somatic diseases, among which the most common are coronary heart disease (CHD), hypertension (HTN), diabetes mellitus (DM), peptic ulcer disease (PUD), infectious and oncological diseases, various types of dermatitis (11). People suffering from psychosomatic disorders usually do not realize and underestimate the role of emotions in their physical manifestations.

We have intentionally chosen various nosological forms of somatic diseases in order to clarify the general mechanisms of the development of psychosomatic disorders in comorbid pathology.

## Methods

The present study is a review of a number of published completed papers by systematically searching original articles in English in the following electronic databases: PubMed, Mendeley, Google Scholar, and ScienceDirect between 2012 and 2022. A manual literature search was also carried out, and the reference lists of the articles found were examined. The main keywords used to retrieve content from these databases were: "psychosomatic disorders", "comorbid disorders", "comorbid psychiatric disorders", "anxiety-depressive disorders", "comorbidity of cardiovascular diseases", "PTSD", "mental health and COVID-19". In addition, we have used Mesh terms as well as truncation, wildcard, and proximity operators to improve the search. The first two authors independently performed searches, checked titles and abstracts, evaluated full-text articles that appeared to be potentially relevant, and selected studies that met the eligibility criteria. In the case of disagreement, a consensus was reached by discussion with other authors.

## Results

248 articles were found by searching the databases. As a result, 60 articles were used. The review includes articles that meet the following criteria: 1) full-text articles, 2) English-language articles, 3) only articles about comorbid psychosomatic disorders. Exclusion criteria: 1) systematic reviews, review articles, writing, conference proceedings, discussion papers, comments, debates, and editorials; 2) articles in languages other than English and duplicates were excluded from the study; 3) articles related to studies involving animals. The initial search strategy yielded 1248 published articles that were selected for possible inclusion in the review. A total of 248 full-text articles were assessed for eligibility, 60 of which were included in the review. The final list of articles was reviewed by two independent authors using full-text articles. In the case of disagreement, they reached a consensus during the discussion.

### *Neurobiochemical mechanisms of psychosomatic disorders*

As is known, somatic and mental pathologies are comorbid processes with similar pathophysiological, neurochemical mechanisms and mediators that affect the functioning of entire body systems (disturbances of the endocrine, immune systems, hypothalamic-pituitary-adrenal axis (HPA axis), associated with depressive disorders. A stressor is a stimulus, internal or external, that activates the HPA axis and the sympathetic nervous system, resulting in physiological changes.

The HPA axis is the central coordinator of the neuroendocrine response systems to stress, and therefore it is the main focus of attention in pa-

tients with psychosomatic disorders. Activation of the HPA axis represents the primary hormonal response to a homeostatic challenge. In acute stress, stimulation of the sympathetic nervous system activates the noradrenergic systems in the brain and causes the release of catecholamines from the adrenal glands, including epinephrine, norepinephrine, and cortisol. Acting as neurotransmitters in the brain, certain catecholamines, such as norepinephrine, can cause a variety of physiological problems, such as altering cognition and other mental processes, leading to poor concentration, mood swings, tension, depression, and anxiety. These substances stimulate the body to respond to immediate danger by increasing heart rate, increasing oxygen distribution to the brain, dilating skeletal muscle blood vessels, and increasing blood glucose levels (hyperglycemia). Hyperglycemia can lead to type II diabetes mellitus and hypertension, which are associated with an increased risk of life-threatening cardiovascular disease (CVD) (12).

The dopaminergic system influences the pathogenesis of many psychophysiological diseases. Dopamine is present in most parts of the central nervous system (CNS), and neuronal pathways, such as the mesolimbic and mesocortical subsystems, play an important role in dopaminergic signaling. The mesolimbic pathway is involved in the processing and amplification of activating stimuli and in the motivation of behavioral responses (13, 14). It is believed that this system is involved in the stimulation of goal-directed behavior, and its inhibition can lead to emotional indifference and lack of initiative. This system has been shown to be highly sensitive to stress (15). The mesocortical pathway is critical for cognitive functions such as the evaluation and planning of behavioral responses. The influence of stressful experiences on the functioning of dopamine in the mesocortical system can be very different or even opposite, depending on the controllability of the situation, the genetic background of the organism and its life cycle.

The biologically active hormone cortisol helps the body adapt to stress. Changes in cortisol levels through the HPA axis lead to persistent detrimental changes in the limbic system. It has been proven that impaired cortisol levels are associated with past stress and depression (16). Thus, excessive secretion of cortisol is observed in about 50% of patients with newly diagnosed depression (17). Since stress causes higher levels of cortisol, cortisol concentrations remain elevated until the cause of stress is removed. What is more, prolonged secretion of cortisol by the adrenal glands can lower immune function, leading to an increased risk of disease.

Serotonin (5-hydroxytryptamine, 5-HT) is one of the main mechanisms in the development of psychophysiological stress (18), which increases the

risk of atherosclerosis (19). The transferred negative emotional states and stress are one of the mechanisms of violation of the serotonergic function of atherogenesis. There is evidence that reduced levels of tryptophan (a precursor to serotonin), and ultimately serotonin, play a role in the pathogenesis of depressive disorders. Serotonin is critical in regulating mood, emotions, and behavior. Preclinical and clinical studies show that depression is associated with CNS serotonergic dysfunction in peripheral circulating platelets (20). Most of the serotonin circulating in the blood is contained in platelets (21). 5-HT has vasoactive properties and is involved in thrombus formation, platelet activation, and hypertension (22). This monoamine, secreted by platelets activated at the site of vascular injury, promotes smooth muscle cell proliferation, vasospasm, and thrombus formation (23).

#### *Genetic and epigenetic factors of psychosomatic diseases*

Additional factors, such as genetic predisposition and epigenetic factors, play a significant role in the formation and development of psychosomatic diseases (24). It is believed that the simultaneous presence of depression and a somatic disease in a patient, described as comorbidity, is not an accident but the result of the implementation of common pathophysiological mechanisms with a high level of genetic influence that increases the risk of their joint (simultaneous or close in terms) manifestation.

The direct contribution of genetic factors to the development of mental illness is very high and, according to various estimates, ranges from 30% to 85%. Hereditary forms of comorbid mental pathologies and somatic disorders are the most severe, rapidly progressive problems, requiring early diagnosis. It is believed that the genetic risk of developing such multifactorial diseases as depression is formed due to the joint (additive) influence of many genetic variants (genetic polymorphisms) of a significant number of genes (25, 26). The most well-studied source of genetic variation known to affect the risk of psychiatric disorders are single nucleotide polymorphisms (SNPs). In the largest whole genome sequencing study of people with and without a clinical diagnosis of depression, 17 independent single nucleotide polymorphisms were identified (27). An even more effective way to predict the development of severe depression is to identify polymorphisms of several genes: the S allele of the 5-HTTLPR polymorphism, the G allele of the 1438A/G polymorphism, and the ValVal genotype of the Val66Met polymorphism in patients with increased levels of anxiety according to Spielberg-Khanin (28). One meta-analysis identified 24 potential genes with possible pleiotropic effects that may be common to both de-

pression and CVD (29). It is likely that depression is not a homogeneous disease and can be caused by various causes. This explains the high comorbidity (up to 50%) of depression with anxiety disorders and various somatic pathologies. The identification of specific biomarkers for the hereditary form of depression may offer approaches to the early diagnosis of these diseases. Predicting the risk of developing such diseases based on genetic testing will be possible if the most significant genetic markers are identified and validated (30). Genetic risk is a "spectral" population phenomenon; each individual in a population has a different level of genetic risk, ranging from extremely low to extremely high.

The next significant part of the multifactorial risk is epigenetic modifications (processes not associated with changes in the structure of genes, i.e., not affecting the DNA sequence but leading to changes in gene expression or cell phenotype). These mechanisms include histone modifications, DNA methylation, and post-transcriptional regulation by non-coding RNAs (RNA-associated silencing), such as microRNAs (miRNAs). Epigenetic changes can be acquired throughout life and mediate environmental influences on gene expression. Evidence is accumulating that differential susceptibility to traumatic stress may be associated with context-dependent functional and transcriptional "epigenetic" changes in various neural circuits, including the hippocampus and amygdala, as well as brain-body interactions, including the HPA axis and the immune system (31, 32). Epigenetic mechanisms are influenced by a variety of factors and processes, including development (both in utero and childhood), environmental chemicals, medications, aging, and diet. An increasing number of studies show the relevance of epigenetic changes in response to traumatic stress throughout life. They provide a possible link between the environment and gene expression, causing specific changes in epigenetic regulation (33, 34, 35). Epigenetic modifications, if they occur at sensitive times in an individual's life, can have long-term effects on the developing brain and ultimately determine the expression of biologically vulnerable genes. Intergenerational studies in animals show that the epigenetic effects of trauma can be passed down through several generations. Therefore, traumatic stress could already affect the epigenetic background of the indicated offspring during pregnancy (36, 37, 38, 39). It is well known that social stress at an early age leads to persistent epigenetic modifications of target genes associated with changes in emotional behavior (40). It must be remembered that the formation of anxiety-depressive symptoms and comorbid somatic disorders also involve the personal characteristics of a particular person and socio-ecological factors.

The psychophysiological health of a person

largely depends on the ability to overcome stress and its negative consequences. Under the same stressful conditions, different individuals exhibit different levels of pathological stress (distress). This fact indicates a different degree of development of self-regulation skills and stress resistance among the participants in the situation. The most significant is the individual psychological characteristics of the individual, how a person "processes" a traumatic event, what are his emotional stability, personal resources and the uniqueness of protective mechanisms. The interaction of emotional stress and a certain personality temperament can increase vulnerability to other risk factors that cause progressive structural adjustment disorders and affect the development of psychosomatic diseases. Type D personality is hypothesized to be a psychosocial factor associated with negative health outcomes. The behavioral stereotype, designated as type D, or "unfavorable personality", is characterized by two global personality traits: negative affectivity and social inhibition (41). Existing evidence has shown that biomedical risk factors such as blood pressure (BP), cholesterol levels, obesity levels, and poor cardiovascular outcomes are significantly associated with type D personality (42, 43). Since 2012, personality type D has been included in the European Guidelines for the Prevention of Cardiovascular Diseases as a risk factor for screening (44). Recent studies have shown an association between Type D personality and depressive symptoms, anxiety, and chronic stress (45, 46). Type A personality is characterized by assertiveness, inability to rest, inability to relax, increased excitability, aggressive desire for leadership, continuous struggle to achieve the greatest result and a high level of competition. It has been noted that in people with type A behavioral traits, the secretory activity of the adrenal medulla predominates due to chronically predominant physiological processes of preparation for the struggle. Among people with behavioral type A, a high level of CVD is characteristic. In addition, cardiac patients with type A behavior are significantly more likely to develop an anxiety disorder according to the DSM-IV than non-cardiac patients, including being more prone to the development of coronary artery disease (47) and causing greater vulnerability to depression.

#### *Psychological stress in cardiovascular disease*

According to the WHO, CVD is one of the main problems in the healthcare system and ranks first in the structure of mortality worldwide (48). Psychopathological disorders are independent risk factors for the development of most CVDs, and also increase the risk of cardiac mortality. Most patients with CVD in real medical practice are characterized by a combination of two or more diseases and conditions, i.e., cardiovascular comorbidity. Thus,

the links between depression, anxiety, and CVD are complex and include psychological, biological and behavioral mechanisms (49). This imposes additional requirements for the observation and treatment of this category of patients.

Among the diseases of the circulatory system, the leading place is occupied by hypertension and coronary heart disease, which have a common pathophysiological relationship. CHD and HTN and associated clinical and metabolic disorders are among the leading modifiable risk factors for cardiovascular disease. In turn, among diseases of the cardiovascular system, the maximum attention is paid to coronary heart disease, which is based on atherosclerosis of the coronary arteries, leading to angina pectoris and myocardial infarction. It is he who leads to angina pectoris and myocardial infarction. The relationship between stress and myocardial ischemia can be explained not only by an increase in the activity of the sympathetic part of the autonomic nervous system, an increase in myocardial oxygen demand but also by an increase in platelet aggregation, atherogenic fractions of lipoproteins in blood plasma, endothelial dysfunction. Another proposed mechanism for the increased risk of CHD associated with depression is chronic inflammation, which is a known risk factor for atherosclerosis and CHD (50).

Psychological stress increases the risk of developing high blood pressure, which also has a positive effect on the high incidence of psychological and behavioral disorders. (51). AH is a pathological, chronic, and progressive disease defined by elevated blood pressure ( $\geq 140/90$  mm Hg). With the progression of hypertension, greater changes in the patient's personality occur, which are accompanied by the accumulation of personal anxiety, which can lead to a depressive state of neurotic origin. In addition, cardiovascular events in people with hypertension tend to appear about five years earlier than in those with lower levels of BP (52). Pathophysiologically, depression and hypertension influence each other, as both shows increased sympathetic tone and increased secretion of adrenocorticotrophic hormone and cortisol (53). Dopamine and other related neurotransmitters have antihypertensive effects; a lack of dopamine in key areas of the brain can increase blood pressure and/or cause depression.

Depression and CVD are two interdependent conditions (54) in which the risk of developing CHD and HTN increases with a certain lifestyle and tragic events. In turn, patients suffering from depressive disorders have an increased risk of sudden death in the presence of cardiovascular pathology. In addition, the presence of depression is associated with an increase in reports of symptoms of dyspnea and/or chest pain in patients with an established diagnosis of CHD (55). The change in heart rate is the most important prognostic indica-

tor both in depression and in the state after acute myocardial infarction. In patients with a comorbid post-infarction state and a depressive disorder, instability of the heart rate is more pronounced, which is the most important indicator of an unfavorable prognosis in patients in the post-infarction period. Depression, arrhythmias, and CHD often occur simultaneously, as they share common behavioral and pathophysiological factors - unhealthy lifestyle, autonomic, HPA axis dysregulation, endothelial dysfunction, and inflammation, which are inextricably linked to each other (56).

#### **Post-traumatic stress and comorbid pathologies in participants in local wars**

On the other hand, about 55-80% of people with clinical depression or anxiety report the presence of traumatic events (57) present in their lives as causative factors in the development of somatic pathology. An important role in the formation of psychosomatic pathology is played not only by psychological trauma but also by post-traumatic stress disorder (PTSD), which occurs as a protracted reaction to a stressful event. PTSD is a mental disorder resulting from experiencing or witnessing traumatic or life-threatening events such as terrorist attacks, violent crime and abuse, war, natural disasters, and serious accidents. On a psychological level, these disorders can lead to irritability in communication, difficulty in performing daily activities and habitual work, loss of interest in life, the constant expectation of failure, a feeling of inferiority, loss of interest in other people, a constant feeling of barely contained anger, a feeling of hostility from the outside, and other psychological problems.

The neurobiology of PTSD is complex and involves neuroendocrine, neurochemical, and neuro-anatomical changes in neural networks. Although the biological, psychological, and social consequences of PTSD have been studied for a considerable amount of time, and treatment has greatly improved due to this, much remains unknown, and controversy persists on both neurobiological and clinical issues. Initially, a diagnosis of PTSD is considered a normal response to an extreme situation. However, the presence of symptoms for an extended period of time in excess of one month indicates an abnormal adaptation in the brain. Extreme situations of professional activity can deplete the protective functional forces of the body of servicemen, reducing the level of its adaptive potential. As with other anxiety and depressive disorders, the main factor in the pathogenesis of PTSD is the disruption of the hypothalamic-pituitary-adrenocortical system (HPAS) - the key mechanism of the body's stress response. A longer stay in PTSD can have numerous pathophysiological effects, such as activation of neuroendocrine (limbic-hypothalamic-pituitary adrenal system) and hor-

monal (corticosterone release) functions.

Increased interest in the problem of psychosomatic disorders in the late period of leaving the combat zone appeared in the 70s when observing Vietnam War veterans. According to a study, approximately 11% of Vietnam veterans over a 40-year period continue to suffer from clinically important symptoms of PTSD, which remains a chronic reality of everyday life (58). The psycho-emotional and neuro-vegetative spheres of servicemen who participated in the Afghan war of the past are subjected to similar tests.

32 years have passed since the Afghan events, and most of the clinical studies on the health status of participants in these tragic events were published in the short term - the first decades. But there are far fewer studies of this problem in the remote period, directly from exposed individuals. The problem of comorbidity among internationalist soldiers who participated in the Afghan armed conflict has so far been practically little studied in both domestic, Russian, and foreign literature. The number of military personnel from Kazakhstan sent to fulfill international duty in Afghanistan in the period from 1979 to 1989 amounted to 21,239 people. Of these, 947 people died, and 1,770 were injured. According to data for 2021, 18,219 internationalist soldiers live in the republic (59), among which there are many participants who became disabled due to severe injuries (up to the loss of limbs) while performing military duties. Currently, this contingent of patients, often with comorbidity, is included in an older age category and, accordingly, deserves close attention and in-depth study of the clinical status. Consequently, involuntional processes, in addition to factors associated with special conditions in this cohort of patients, are naturally reflected in systemic disorders of the body. A very important aspect, in practical terms, is to clarify the relationship between violations of psychophysiological and neuro-vegetative rearrangements in the formation of PTSD in combat veterans.

The ten-year war contributed to the development of psychic trauma against the background of emotional events (exposure to ultra-high stress situations, injuries, and shell shock in war veterans), which led to the development of anxiety and depressive disorders along with cardiovascular pathology. An analysis of data from a nationwide representative epidemiological study showed that 6.5% of PTSD was caused by a somatic disease (60). CVD and anxiety-depressive disorders, are among the most common diseases leading to premature disability and death among the adult population and internationalist warriors in particular. Currently, no more than 10% of military personnel with psychogenic disorders seek medical help, although the proportion of patients who need it is much larger. This increases the importance of

early pre-nosological diagnosis of PTSD in the pathogenesis of CVD. According to the data, the incidence of CHD over 8 years of follow-up increased by 63-93% in internationalist soldiers with PTSD after participation in the military conflict with Afghanistan and Iraq (61). The Russian KOMET study showed that symptoms of anxiety and depression were present in half of the outpatients with HTN and CHD, clinically pronounced anxiety symptoms were detected in 25.5%, and depressive symptoms in 16.3% of patients, which indicates the need to identify and correct anxiety and depressive disorders in clinical practice (62). In one of the studies by the co-authors of this review, Tatayeva R.K. and others, an analysis of the incidence of 675 patients who were hospitalized in a hospital for war veterans was carried out. A higher incidence of CVD-AH (55.6%) and CHD (33.0%) comorbidities was established in people who were in special conditions of a man-made, environmental disaster or participants in hostilities in remote periods (63). The influence of prolonged combat stress creates favorable conditions for the maintenance of HTN and the initiation and progression of the atherosclerotic vascular process. As a result, it can lead to a violation of the regulation of homeostasis in the human body and subsequently to desynchronization. This distress leads to the disruption of circadian biorhythms, hormonal changes, and normal heart rhythms. It has been shown that people suffering from PTSD experience an increase in heart rate and BP (blood pressure) in response to stimuli such as loud noises similar to gunshots during military combat (64). Over time, people who experience chronic stress on the heart may develop risk factors for heart disease, such as high blood pressure. These symptoms significantly worsen the daily lives of combatants. Therefore, it is extremely important to preserve the health of war veterans and adapt to the conditions of civilian life.

#### *COVID-19 as an additional stressor*

The COVID-19 outbreak in December 2019 has created additional stressors that further affect the mental health and well-being of the general population, making them vulnerable to psychological distress (65). It is known that every third person who has recovered from COVID-19 suffers from a nervous or mental disorder. In the Islamic Republic of Iran, phenomena such as anxiety and confusion were observed among the population. A qualitative analysis of the data obtained showed that most of these emotions were the result of low awareness or misinformation (66). Apparently, the adverse impact of COVID-19 on the national economy and subsequently on the daily life of people has led to increased feelings of despair and hopelessness in society and in some cases, even led to suicidal thoughts (67). In Russia, during the

pandemic, the number of people who applied for psychological or psychiatric help increased from 10 to 30%, depending on the region. Studies have shown that the relationship between the coronavirus pandemic (the risk of contracting the virus along with appropriate measures taken to combat it) and severe stress and anxiety has resulted in poor psychological well-being (68), increased suicidal tendencies (69), irritation of pre-existing mental health conditions (70). During a pandemic, the number of people suffering from mental health tends to be higher than the number of people affected by the infection (71). Previous research has shown that the prevalence of emerging infectious diseases can increase levels of anxiety, depression, and stress in the general population (72). The results of the study show that anxiety and stress are high in isolated people (73). In addition, an overabundance of information about the pandemic and its consequences, social distancing, and closed social and educational institutions are among the main mental health problems of the population. Studies have confirmed the impact of COVID-19 on the negative change in the psychosocial state of students (74). Another aspect is the importance of the mandatory immunization program for the population. Today, vaccination is a very safe and effective way to fight infectious diseases, but the effectiveness of a vaccine largely depends not only on its mechanism of action but also on the characteristics of the vaccinated person. Psychological, social and behavioral factors can significantly influence the response of the immune system, so psychological factors shape the antibody response to vaccines even in young and healthy people (75). In addition, the effectiveness of the vaccine is not only reduced but also causes more immediate and temporary side effects such as fatigue and bad mood. For example, the inflammatory reaction, which is the first link in the immune response, usually lasts for several days but may last longer in people who are depressed. In a large representative sample from the United States, people with increased fear of COVID-19 were at a particularly high risk of clinically significant depressive symptoms (76). Being able to avoid exposure to stress during vaccination can help reduce the chance of unpleasant side effects. In addition, a category of the population with a low socioeconomic status (lack of food security), exacerbated by the pandemic, was at particular risk (77). These complex interactions are thought to provide the conditions for identifying or avoiding experiential and physiological components of emotional mechanisms that may mediate psychosomatic illness.

### Conclusion

Thus, the mechanism of common biological components with a genetic basis is involved in the formation of psychological symptoms and comor-

bid somatic disorders. This suggests that under certain conditions, both one disease and a cluster of disorders with different phenomenological characteristics, united by common genetically mediated pathophysiological mechanisms, can manifest. Comorbid mental and somatic disorders are often recognized too late and limit or complicate the treatment and diagnostic process because specialists without psychosomatic experience lack simple diagnostic tools for their accurate detection. This determines the high social significance and the need for continuous improvement of the system, means and methods of prevention, correction of the psychosomatic state and rehabilitation measures, as well as early detection of risk factors and initial manifestations of diseases. With the correct correction of the psycho-emotional status, it is possible to improve the quality of life of patients and reduce the risk of adverse complications.

### Conflict of Interests

The authors declare that they have no competing interests.

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