BRZUSZKIEWICZ, Kinga, RUDZIŃSKI, Gracjan, ŁOZOWSKI, Borys, RACZKIEWICZ, Przemysław, KUSAK, Natalia & SOROKA, Ewelina. The role of environmental factors in the etiology of schizophrenia. Journal of Education, Health and Sport. 2023;23(1):52-70. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.23.01.006
https://apcz.umk.pl/JEHS/article/view/43381
https://zenodo.org/record/7861500

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.04.2023. Revised: 10.04.2023. Accepted: 24.04.2023. Published: 24.04.2023.

The role of environmental factors in the etiology of schizophrenia

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Keywords: hypothesis of schizophrenia, schizophrenia, environmental factors

Abstract

Introduction: Schizophrenia is a psychotic disease characterized by multifaceted psychopathology. To date, research has shown that it is an inherited disease and significant progress has been made in identifying genetic risk factors.

Methods: This paper summarizes the current and most recent findings on the role of environmental factors, and demonstrates the continued need for more in-depth research to better understand how this type of disorder occurs.

Results: Recent studies show that 15-40% of the risk that comes from environmental sources is not fully understood. Environmental factors that have been repeatedly studied and have been proven to influence the development of the disease include: obstetric complications, infections, childbirth in the winter or spring month, living in the city, severe childhood events or marijuana use.

Discussion: Schizophrenia is a devastating mental illness that remains poorly understood. A full picture of how genetic and environmental risk factors affect the risk of developing schizophrenia requires an understanding of the interactions between them. It should be taken into account that for this disorder, the interactions between genetic and environmental risk factors are also not well understood and deserve further research in the future.

In the case of schizophrenia, the interactions between environmental and genetic risk factors are not well understood and still require further research. Elucidating the mechanisms underlying the disease is extremely important, as it may have an impact on taking measures to prevent the development of the disorder. In addition, their discovery will help improve treatment. In conclusion, it is important to emphasize the need for further research to better understand the impact of environmental factors on the development of susceptibility to a mental disorder such as schizophrenia.

Schizophrenia is a disorder characterized by symptoms that distort basic functions of the human mind, such as perception and memory. This makes it difficult for sufferers to control reality. This can have serious consequences, both for the affected person and society. More than 100 years have passed since Emil Kraepelin [1] first attempted to describe schizophrenia as "dementia praecox," and many studies have been conducted.

In defining it, Emil Kraepelin relied on two elements: the age of onset (praecox), as well as the final stage (dementia) of the course of the disease, which he called dementia. Another scientist who took up the study of schizophrenia was Eugen Bleuler [2]. A Swiss psychiatrist, he expanded the diagnosis of the disorder and replaced "dementia praecox" with "schizophrenia." However, neither term is a fully accurate description of the complex nature of the disorder. After giving the disorder a new name, Eugen Bleuler also introduced auxiliary terms, the so-called 4As, designed to clarify and better illustrate the pathology involved. The 4As include autism, ambivalence, association disorder, association, and pale affect.

Schizophrenia affects about 1% of the population [3], and the annual incidence is about 0.20/1000/year [2]. The disorder is more common in men. It begins in the late teenage years or early twenties. It is associated with significant morbidity and premature mortality. The mortality rate is 2.5 and the mortality rate is 5% [4]. Schizophrenia is characterized by positive symptoms such as delusions and hallucinations and negative symptoms such as pale affect, alogia and avolition. Delusions and psedohallucinations are present in virtually all cases of the disease [5]. Difficulties in social interaction and communication, may be evident even in the early stages of this disorder. They impair daily functioning to a significant degree [6].

Genetic factors are a significant factor in increasing the risk of the disease. In monozygotic twins, the risk is about 64-81% [7,8]. Environmental factors also play a significant role. In addition, among mental illnesses, the greatest correlation is between schizophrenia and active bipolar disorder. In a study conducted by Lichtenstein and co-authors in 2009, the correlation was as high as 0.6-0.68 [9]. This correlation has also been confirmed by other studies [10,11,12]. A study of the entire human genome found as many as 270 single nucleotide polymorphisms causing schizophrenia. The same study found a link between bipolar disorder and schizophrenia [11,12].

Researchers have also conducted many studies to find gene loci that influence the development of the disorder. Several potential sites that could contribute to its development have been identified. However, these studies were not sufficient to find a significant correlation [13]. Further genome-wide studies, including whole-genome sequencing (WGS) studies, are planned in future years, which are likely to investigate rare gene variants [14].

Past studies of families with schizophrenia have proven that several loci can potentially affect synapses and neurocognitive performance [15]. In addition, variations in genes related to metabotropic glutamate receptor 5 (mGlu5) have been shown to be much more common in affected family members [16].

The above-mentioned studies do not explain all the factors in the development of schizophrenia. Further on this issue there are a lot of inaccuracies and insinuations. In this paper, I will try to systematize the environmental factors and their impact on the development of the disease.

Obstetric complications

In research studies, complications during pregnancy or childbirth have been associated with the later development of schizophrenia in the offspring [17]. Factors that affect the prenatal and early postnatal period significantly affect the brain. The most important feature is oxygen deprivation. A study in Sweden showed the effect of fetal hypoxia on the development of schizophrenia [17,18]. Its occurrence in the perinatal period was associated with a more than fourfold increased likelihood of developing the disease [18]. A Danish study also found an association between hypoxia, prematurity and schizophrenia [19].

In contrast, in a study conducted in the United States, those with perinatal hypoxia and environmental factors were more than five times more likely to develop schizophrenia than those with hypoxia but no environmental factors [20]. In addition, it is worth noting that the negative effects of fetal hypoxia are most pronounced in children who have a low gestational age [17]. Environmental factors such as maternal stress during pregnancy and perinatal infections may be related to the development of schizophrenia in the future [20]. Subsequent studies have proven that perinatal hypoxia vs. the risk of developing the disease is higher in individuals with correspondingly higher genetic risk [21], as confirmed by sibling studies and the occurrence of higher genetic risk in twins with hypoxia, where one of them developed schizophrenia [20].

A 2018 study found an association between obstetric complications and SNP expression in placental tissues [22]. Subsequent work, however, found insufficient evidence for this link [23]. In 2008, an interaction was admittedly found for three SNPs within AKT serine/threonine kinase 1 (AKT1) [24]. This was also replicated in another paper, but only in women [25].

Infections

A growing body of evidence points to an important involvement of the immune system in the etiopathogenesis of psychiatric disorders. Several infectious agents, including viral, bacterial and parasitic infections, have also been linked to the onset of schizophrenia [26].

Genes related to B lymphocytes involved in acquired immunity like CD19 and CD20 lines, as well as the major tissue compatibility system have been linked to schizophrenia [27,28]. Subsequent studies have shown overactivity of complement, particularly factor C4 in mediating the elimination of synapses during postnatal development [29]. It should be noted that immune signaling also changes during puberty. Many changes in neurotransmitter release across the blood-brain barrier (BBB) occur then [30-33]. In addition, there is a theory that

schizophrenia is correlated with intestinal changes and blood-brain barrier function [34]. This suggestion, combined with the altered microglia in patients with psychosis, underscores how important a role the human immune system plays.

It is difficult to answer what type of infection, has the greatest affinity towards the development of a disease like schizophrenia. This is because when studying different groups, many factors must be taken into account, such as exposure time, virulence and methods of assessing the infection.

This can hinder homogeneity and reproducibility of results. The strongest evidence of correlation involves Toxoplasma gondii [35]. Infection is associated with processes, occurring in the body, such as increased dopamine production [36]. The appearance of changes in character has also been documented, that is, increased aggression, impulsivity [37] and risk of traffic accidents [38].

The timing of infection is also important. Pre- or perinatal induction of an immune response can be particularly damaging. A landmark study was the 1957 influenza epidemic in Finland. Pregnant women exposed to the virus in the second trimester had offspring with an increased risk of schizophrenia [39]. Subsequent work confirmed a significant association with the influenza virus and the development of the disease later in life [40]. Bacterial infection in the mother during pregnancy was also associated with psychosis in the offspring. The risk was higher in male individuals [41]. A Danish study supported the claim that exposure to any bacterial infection during the first trimester increases the risk of schizophrenia [42].

In contrast, when viral infections of the central nervous system (CNS) occur in childhood, it results in a 2.1-fold increased risk of schizophrenia in adulthood. Moreover, no significant increase was observed for bacterial CNS infections [40]. These findings were further supported by a large Swedish study involving more than one million people that examined the impact of childhood CNS infections on the development of the disease. No evidence was observed to support the role of any bacterial CNS infections, but two viral infections, namely mumps virus and cytomegalovirus, were associated with the development of later psychosis in patients [43]. In addition, it was proven that the number of infections was significantly higher in people living in cities than in rural areas [44-46].

An important fact is that when studying infections in later life, the timing of the infection should be considered to establish a link to the effect. People with schizophrenia tend to have higher morbidity and many additional factors that further increase their susceptibility to infection [44]. Other elements associated with increased risk of infection include stress, social inequality and living in a large city [45,46].

One of the main mechanisms underlying infection is inflammation. Inflammatory processes can affect neuronal pathways and neurotransmitter reuptake (such as serotonin, norepinephrine, and dopamine), as well as stimulation of the hypothalamic-pituitary-adrenal (HPA) axis [47]. Decreased innate immunity can result from an innate genetic predisposition, occur after conception, or be a combination of both. For example, the "two-hit" hypothesis [48] infers that genetic or environmental factors early in life (the first hit) disrupt CNS development and increase susceptibility to a "second hit" later in life [49]. "Stroke" environmental factors can result from causes such as CNS infections or result from systemic inflammation in response to any infection in the body [50]. Research papers have identified

correlations between autoimmune diseases and psychosis, which argues that there may be common inflammatory features within them [51,52].

In contrast, studies in Scandinavian countries that analyzed family history of the disease did not generally show an increased risk of psychosis in offspring after maternal infection alone during pregnancy [53,54]. Only in mothers with psychiatric disorders and infection during pregnancy, there was a statistically significant increased risk of psychosis for offspring [54,55].

Some work by researchers, have put forward the suggestion that genetic variation that is involved in the immune response may underlie susceptibility to certain infections, and this in turn increases the risk of schizophrenia [56]. In another study conducted in Denmark, a strong genetic correlation was found between susceptibility to infections and psychiatric disorders [57]. It has been discovered that variation in the MHC region, which is associated with susceptibility to infectious diseases [58], has been repeatedly linked to schizophrenia in many studies in the past [59,60].

A genome-wide study proved that an interaction between SNPs in the CTNNA3 gene region and CMV infection in the mother increases the risk of schizophrenia in the child [61]. Another study found that maternal herpes simplex virus 2 (HSV-2) interaction with GRIN2B also increases the risk of the disease [62].

In conclusion, these studies show that infections may play a direct or indirect role in causing schizophrenia. Interestingly, it has been shown that there may be a genetic correlation between infections and psychiatric disorders. This, in turn, shows that there is a possibility that genes related to immunity, which is involved in the response to infections, are risk genes for mental disorders. If this is the case, it could be argued that they act in a similar way to genes related to nicotine addiction, which significantly increase the risk of lung cancer in people who actively consume tobacco products [63].

In addition, it is worth mentioning that numerous studies have shown a higher incidence of the disease in people born in the winter and spring months [64,65]. The risk was significantly higher at higher latitudes, which are subject to seasonal variation [66]. It should be emphasized that it is the seasonal variability of exposure to viruses, especially influenza, that may determine the association between schizophrenia and births at the beginning of the year. There is also evidence of a significant interaction between the cytokine IL-4 and the time of birth with a milder diagnosis of schizophrenia spectrum disorder [67].

The aforementioned studies are consistent with the hypothesis that the association between time of birth and schizophrenia may be mediated by many other environmental risk factors. Although infections are the most cited factor, other factors should also be kept in mind, such as complications of pregnancy and childbirth, exposure to sunlight, nutrition, temperature, weather, or a combination of all the above.

Migration

Several studies have found an increased risk of mental disorders, particularly schizophrenia, in migrants [68]. Second-generation migrants were the most likely to develop the disorder, suggesting that the increase is not solely due to experiencing the stress of the

change of residence itself, but to the many social and environmental differences that accompany it [69].

It has been shown that multiple factors occurring simultaneously can contribute to increased risk in migrants, such as social factors, for example: socioeconomic disadvantage and discrimination by society [70]. Interestingly, migrants are more likely to have inadequate vitamin D levels [71] or a greater propensity to develop infections [72]. One of the main theories explaining this condition is the hypothesis that social stressors, which are more common in marginalized, socially excluded or minority groups, may increase the risk of developing psychosis [73]. Migrants from Africa moving to places like Sweden, France and Canada have the highest risk of psychotic disorders [74,75]. Finnish migrants in Sweden have twice the prevalence of schizophrenia [76]. A suggestion has been made that risk can be attempted to estimate the level of discrimination in a country [77], indicating the important role of society in an individual's risk of developing a mental disorder. Other problems faced by migrants should also be considered, including health care difficulties, errors, and diagnostic misunderstandings due to language and cultural differences.

Place of residence

It has been confirmed that there is an increased risk of schizophrenia in people living in urban areas compared to more rural areas [78]. This study hypothesized the influence of elements such as, social environment (e.g., economic stress) or physical environment (e.g., air, noise, or pollution), which require further research [79].

Colodro-Conde and co-authors came to the interesting conclusion that people with increased genetic susceptibility to schizophrenia tend to live in more densely populated urban areas. Similarly, a study conducted in Denmark showed. People with a higher risk of developing schizophrenia were more likely to live in the capital city compared to other rural areas [81].

In a large cohort study of children from the UK's Avon Longitudinal Study of Parents and Children (ALSPAC), there was an association between schizophrenia and neighborhood deprivation - but not necessarily in more densely populated areas [82]. A Swedish study showed a similar relationship supporting the genetic selection theory that genetic risk for schizophrenia predicts where one lives in poor neighborhoods [83]. Thus, the study shows that the risk depends on the gene-environment correlation, that is, people with a higher genetic risk of the disease are more likely to choose to live in urban environments. The above studies indicate that further work will be needed to further investigate urban living and the extent to which these correlations are driven by genetic risk factors [84].

Childhood experiences

Adverse childhood experiences have been subjected to many studies. Their positive correlation has been proven [85,85,87]. They include stressful life events, trauma experienced in childhood and poor socioeconomic conditions. The definition is very opaque, as it includes many problems such as financial difficulties, parental separation, neglect, physical or emotional abuse, or the death of a family member [88]. The risk is usually highest for very serious stressful events, such as the death of a first-degree relative [89].

Loss of parents is associated with psychosis in offspring regardless of family history of mental disorders [88]. Offspring of deceased suicidal parents are more likely to commit a suicidal act (as well as psychotic disorders, substance abuse) [90]. Even children of parents with milder mental illnesses are more likely to experience similar problems [91], adding to the difficulty of identifying a significant correlation.

It is worth emphasizing the fact that the genetic and environmental effects of childhood trauma can act independently [92]. However, in individuals at high risk of developing schizophrenia, exposure to childhood difficulties was associated with greater expression of psychosis [93].

Researchers have observed a reduction in brain-derived neurotropic factor (BDNF) levels. Its role is to promote the growth and differentiation of neurons during brain development. It is also responsible for so-called synaptic plasticity, and thus for the state of neurons in adulthood [94]. Interactions between childhood trauma experience and the BDNF gene in relation to schizophrenia have been repeatedly confirmed in studies [95,96]. Similarly, childhood abuse has been reported to correlate in the later development of psychosis [95], but this hypothesis has not been replicated in subsequent work [96].

Marijuana

Several studies [97] have found that cannabis use was associated with an increased risk of psychosis and the onset of schizophrenic symptoms in later life. Other work has reported that cannabis use is associated with the development of the disease [98].

Although cannabis use is often accompanied using other active agents, prolonged consumption of cannabis is associated with a higher risk of psychotic symptoms [99]. Other substances, that is, cocaine or other stimulants, have also been found to be associated with the development of schizophrenia [100]. Correlations between drugs may be due to genetic predisposition or shared neurological pathways [101]. There are relatively few studies that undertake an analysis of the relationship between illicit substance use and psychosis. This is likely since they are based on self-reported data. Another problem is the difficulty in quantifying exposure, that is, dose, purity of preparation and frequency of use. Cannabis is currently the most widely consumed recreational drug according to 2018 World Health Organization (WHO) data [103], so understanding the mechanisms underlying its link to the development of psychosis would have the greatest stake in minimizing harm in the future.

Giordano et al. in 2015 found that cannabis abuse (as determined by physician diagnosis and possession convictions) seven years prior to schizophrenia diagnosis was associated with a 2-fold increased risk of developing the disease [102]. Other researchers have found that in individuals with no history of psychotic experience, regular cannabis use during adolescence preceded the onset of psychotic symptoms [99]. In addition, it is noteworthy that continued use of the substance is associated with higher rates of relapse in patients with psychosis [104].

Another study, conducted on a group of 2,082 healthy individuals with risk factors for developing schizophrenia, showed an association with cannabis use [105]. This means that people with risk factors for developing the disease, are more likely to use stimulants. This finding was confirmed in a study of twins. It showed that the burden was highest when both

twins were cannabis users and correspondingly was lowest if neither of them reported using cannabis.

French and co-authors in 2015 examined the risk of cannabis use and subsequently performed brain imaging studies in 1,577 individuals (in three populations of adolescents and young adults). The results showed that a higher risk of developing schizophrenia was associated with reduced cortical thickness, but only in male individuals who additionally used cannabis. It is worth noting that as we age, changes occur in the brain. The gray and white matter begin to differ in women and men [107].

Studies show that cannabis use alone is not a sufficient trigger for psychosis in the general population. Instead, it can trigger a mental disorder in susceptible individuals. In a study conducted in siblings, it was proven that there is an important interaction between cannabis use and an SNP located in the AKT1 gene. Its function is to encode a protein kinase, which in turn occurs in the dopamine cascade. It has been proven to be associated with a twofold increased risk of being diagnosed with a mental disorder in the future [108]. Subsequent studies have identified an interaction between cannabis use and COMT gene variation in psychosis [109,110].

It should be emphasized that additional studies on a larger number of patients will be necessary in the future. Then it will be possible to assess the impact in a conclusive manner. In summary, a few research papers suggest that cannabis use affects the development of the disease, but it should be emphasized that this influence interacts together with genetic and familial factors [106,111].

Other risk factors

Air pollution is a well-known adverse environmental factor. It poses a threat to human health and is also a carcinogen. Its effects go beyond respiratory diseases and cancer [112]. It is also a risk factor for the development of such neurological diseases as Parkinson's and Alzheimer's disease, for example [113]. Mechanisms involved in the body's response to polluted air include oxidative stress, systemic inflammation, and nervous system inflammation, among others [114,115]. Therefore, we may suspect that there is a link between air pollution and other disorders, such as schizophrenia. In Denmark, it was proven that exposure to higher concentrations of nitrogen oxides in childhood was associated with the development of schizophrenia in the future [116]. In Sweden, on the other hand, high air pollution was associated with increased medication dispensed for mental disorders in children and adolescents there [117]. In China, even short-term exposure to any ambient air pollution has been shown to be associated with a significantly higher number of daily outpatient visits for schizophrenia in adults, both in those with and without a prior diagnosis of the disease [118]. A recent study assessing the level of risk associated with various types of environmental pollution was conducted for 151 million people in the United States and 1.4 million people in Denmark [119]. In this work, an association between air pollution and the subsequent development of schizophrenia was proven. Although this is the largest and most thorough study to date on air pollution, it should be emphasized that more evidence is required before this risk factor can be conclusively established yet.

Cigarette smoke is also an air pollutant and has ample evidence of negative health effects. There are studies that indicate its effects on the development of schizophrenia [120]. The effects are not limited to the inhalation of chemicals in tobacco smoke, as there is ample

evidence of a link between non-affective disorder and smokeless tobacco [121]. In addition, they confirm a common genetic relationship between smoking and psychosis [122] and have shown a correlation between genes in schizophrenia and cigarette addiction [123]. The growing number of new publications may mean that nicotine will soon gain much more recognition as a risk factor for schizophrenia [121-123].

Brain damage often precedes the onset of several psychiatric conditions, including schizophrenia [124,125]. In a study of siblings before they reached the age of 25, siblings who experienced brain injury had twice the risk of future psychiatric hospitalization [126]. However, it is not known whether they had an overall higher genetic risk of psychiatric disorders than their siblings without injury. With too few studies on the subject, a link cannot be clearly established. Therefore, it is extremely important to conduct further research work addressing this issue.

Hearing impairment in childhood has been described as another risk factor for the development of psychosis in adolescence [127] and later in life [128]. However, despite several of the aforementioned papers, there is no clear evidence of an interaction with schizophrenia [129]. The small number of reports on this topic makes it difficult to assess the rationale for this potential link.

There is growing interest in nutrition and the relationship between deficiencies in certain nutrients and the development of psychiatric disorders [130]. For example, folic acid is a very important nutrient, and there is ample evidence of decreased serum folic acid levels in people with schizophrenia [131,132]. Polymorphisms of the methylenetetrahydrofolate reductase (MTHFR) gene, an enzyme involved in the folic acid cycle, may only fragmentarily support this link in the development of the disease [133,134]. Another example is vitamin D, which is produced when the skin is exposed to sunlight and obtained from food [135]. Low vitamin D levels have been linked to the development of schizophrenia [136]. This is supported by, among other things, two scientific studies that proved a correlation between vitamin D deficiency in newborns and the development of the disease [137,138]. The same work detected a link between births in the winter and spring months and the risk of schizophrenia because there was too little maternal exposure to sunlight. A link between vitamin D and the development of a disorder such as schizophrenia was also shown in the case of migration of dark-skinned individuals. By moving from areas with higher levels of sunlight to areas with less, they were at greater risk of developing the disorder [139].

Cytokine levels

Higher levels of cytokines in some diseases affect changes in the mechanisms involved in immunity. Many research papers confirm the change in cytokine levels in schizophrenia. Higher levels have been found in: IL-1β, sIL-2R, IL-6, TNF-α, TGF-β and CRP in the blood [140]. IL-17 levels have been shown to undergo changes in acute episodes of psychosis. There is also evidence that IL-23 is significantly elevated during schizophrenia. Moreover, it is noteworthy that high levels of IL-23 also persist during treatment [141].

Reduced IL-6 activity, on the other hand, is associated with an increased likelihood of developing schizophrenia in the future, and leads to another disorder such as metabolic syndrome, further indicating the interrelationship between schizophrenia and metabolic dysregulation and co-occurring inflammation [142]. Additionally, other studies confirm that CRP and IL-6 protect the body from developing schizophrenia [143].

The above studies conclude that the immunological and metabolic changes underlying schizophrenia are an extremely important component of the disease, which can often precede clinical diagnosis.

Age of mother and father

Research papers have found a higher risk of schizophrenia in offspring of mothers aged ≥ 40 years [150], and a much lower risk in offspring of mothers aged > 30 years [151]. Another study also confirmed an increased incidence in mothers aged > 34 years [152]. More conclusive results emerged for the age of the father, occurring at birth. A high chance of developing schizophrenia was found when the father's life expectancy exceeded 30 [153] or 34 years [154].

Level of education

A low level of maternal education increases the risk of developing the disease [155,156]. So far, only one study has indicated that the father's not very high education may have an impact [157].

Family factors

Several studies have documented an increased risk of schizophrenia in people with poor family relationships, that is, parent-child (in that ties were described by patients as: "unsatisfactory" or "bad") [158]. An absent father is another factor [159]. In other work, researchers found that problems in adjusting one's behavior (poor relationships within the family, relationships with peers, and confirmed destructive behavior at school) increased the risk of schizophrenia [160].

Microbiome

There is growing evidence of gut-brain axis dysfunction that occurs in patients with the disease. One of the main causes of this dysfunction is changes in the gut microbiome. A hypothesis has been put forward that dysbiosis is a factor in the development of schizophrenia [144].

The gut microbiome may mediate the proper functioning of our nervous system through the gut-brain axis. It has been found to be significantly affected in schizophrenia [145]. The fact that both untreated and treated schizophrenic patients have a low diversity of the microbiome has been proven [146]. Moreover, in scientific papers, it has been shown that fecal transplants from mice diagnosed with schizophrenia to individuals free of the disorder caused large changes in the brain, that is, altered levels of glutamine and glutamate in the hippocampus have been reported [147]. This mechanism can lead to changes in the levels of bacteria that are involved in stimulating the body's response. Consequently, this leads to chronic inflammation, which may be linked to schizophrenia [148,149].

The study found an increase in IL-6, IL-8, TNF-α, which are known inflammatory factors. There has been a decrease in factors that counteract the aforementioned cytokines, such as IL-10 [161]. A correlation between IL-6 levels and the development of psychosis has

been proven in works [162,163]. Its high concentrations occurred during the acute state of schizophrenia. In contrast, during treatment, they decreased accordingly.

In addition, an increase in markers of intestinal inflammation was noted. One of them is antibodies to Saccharomyces cerevisiae (ASCA), which is a marker of Crohn's disease. It has been shown that significantly increased ASCA titers correlate with the development of schizophrenia [164]. Another study confirmed this fact. Patients who were diagnosed with this disease and did not receive treatment had high levels of these antibodies [165].

Dysbiosis causes increased intestinal permeability, and this in turn contributes to systemic inflammation, which is associated with psychiatric disorders [166].
Subsequent work has examined the gut microbiota to detect differences in gut bacteria. A significant increase in pathogenic bacteria such as Megaspharea, Clostridium, or Klebsiella and a decrease in Coprococcus or Roseburia were observed. The latter are involved in the formation of butyrate, which accelerates intestinal regeneration and healing [166].

One further finding is a significant increase in Lactobacilli in people with schizophrenia, as well as in those who have an increased risk of developing the disease. This causes an increase in the intensity of symptoms of the disease in these individuals [167]. This is an interesting finding. Lactobacilli are frequently used, and are components of probiotics, which most people associate with positive effects on our bodies and health. In addition, subsequent work shows that treating schizophrenic patients with antipsychotic drugs also causes changes in the microbiome. In rodents, olanzapine increased Firmicutes and decreased Bacteroidetes [168,169]. Studies in humans have also shown this relationship [170-174]. This is likely due to the fact that any treatment affects the microbiome and can also weaken it. In the future, the discovery of agents that improve the composition of the gut flora could help treat schizophrenia.

One study of 3409 people with schizophrenia found that 1,549 had been exposed to an infection in the hospital, just prior to the diagnosis of the disease, accounting for as many as 45% of the subjects [172]. The highest risk was proven for bacterial disease of the liver and genitals [175].

Another study of 1.2 million people showed that the occurrence of a central nervous system (CNS) viral infection was associated with a twofold increase in the risk of schizophrenia in adulthood [173]. Interestingly, this study found that CNS bacterial infections were not associated with an increased risk of psychosis onset [174].

In conclusion, the analysis of the microbiome in people with schizophrenia spectrum disorders is very promising. Studies have shown a large impact of gut microbiota and inflammation on people with psychiatric disorders.

Summary

In the case of schizophrenia, a very strong link has been shown between the above-mentioned factors such as obstetric complications, migration, cannabis use, and infections. Recent research evidence points to other elements that affect our bodies, such as air pollution, smoking. It should be noted that although the disease was described many years ago, only a small part of the environmental factors to which people are exposed have been studied, and

with further scientific work, it is likely that more determinants of the development of a condition like schizophrenia will be added.

Analysis of the gender of the person with the disease also has important differences. These have been studied many times, but rarely in relation to environmental risk. Studies have proven that cannabis use is more frequently reported, as well as an increased incidence of infection in men early in life. Moreover, even the immune response varies by gender. Future studies would therefore need to assess separately (on women and men) the impact of environmental factors.

In addition, it is important to remember that many factors can interact with each other. For example, survivors of childhood trauma are more likely to use cannabis [176]. Another example could be the higher exposure to infections in more densely populated populations, such as cities. In view of the above examples, familial and environmental factors may have a joint effect in increasing the risk of disease onset.

With genetic factors, it is easier to determine risk than with environmental elements. Genetic factors are better established and reproducible. Therefore, it is easier to discover a correlation. In addition, numerous genes that increase the development of the disease have been revealed. An element hindering the study of a significant relationship between factors and the development of schizophrenia, is the disproportionate number of people of European descent in genetic studies [177]. In addition, it is worth noting that many psychiatric disorders are characterized by a common genetic risk. This makes it likely that emerging environmental factors may be important elements that determine disease triggering [178].

In the research included in this paper, various types of scientific studies were reviewed. These ranged from population-based cohort analyses to cross-sectional papers with assessments of exposure to a given agent. The reported differences in both the timing of exposure, measurements and resulting outcomes in the development of psychiatric disorders makes it difficult to interpret which factors clearly and unequivocally and to what extent influence the onset of the disease.

In the case of schizophrenia, the interactions between environmental and genetic risk factors are not well understood and still require further research. Elucidating the mechanisms underlying the disease is extremely important, as it may have an impact on taking measures to prevent the development of the disorder. In addition, their discovery will help improve treatment. In conclusion, it is important to emphasize the need for further research to better understand the impact of environmental factors on the development of susceptibility to a mental disorder such as schizophrenia.

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