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The incidence of schizophrenia in the context of growing up in urbanised vs. green areas – a narrative review

Zapadalność na schizofrenię w kontekście dorastania w środowisku zurbanizowanym lub w obszarach zielonych – przegląd literatury

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Abstract

The neurodevelopmental theory of schizophrenia describes multiple risk factors of this serious mental disorder. These include genetic factors that generally have biological roots, as well as factors related to the upbringing in a specific environment during childhood and adolescence of a person who will develop schizophrenia in adulthood. The neurodevelopmental hypothesis also implies the existence of protective factors. The paper discusses selected environmental risk factors and protective factors of schizophrenia in the context of ecopsychiatry. Urbanicity has for decades been a factor indicated as one that increases the risk of schizophrenia. Contemporary research helps understand how growing up in an urban environment affects brain development, with a particular focus on grey matter volume changes in the dorsolateral prefrontal cortex and the perigenual anterior cingulate cortex. The impact of air pollution as a risk factor for schizophrenia is also the subject of discussions. Exposure to outdoor air pollutants containing particulate matter and ultrafine particulate matter, gases, organic compounds, and metals can lead to neurotoxicity and neuropathology. Air pollution can affect the brain through such mechanisms as inflammation and oxidative stress. On contrary, higher exposure to green spaces has been suggested to reduce the incidence of schizophrenia. Some research indicates a dose-response association between the level of exposure to green space in childhood and a lower risk of developing schizophrenia in the future. The presented review of selected publications indicates that exposure to a certain environment in childhood and adolescence modulates the risk of schizophrenia. Environments heavily transformed by human activity (urbanisation) and characterised by a high level of chemical contamination (toxins, air pollution, smog) are a risk factor for schizophrenia. Protective factors, on the other hand, include direct contact with the natural environment from childhood through adolescence to adulthood.

Keywords: schizophrenia, incidence, risk factors, neurodevelopmental theory, air pollution, urbanity, natural environment

Streszczenie

W kontekście teorii schizofrenii jako zaburzenia neurorozwojowego opisano liczne czynniki ryzyka wystąpienia tej choroby. Niektóre z tych czynników mają charakter biologiczny, inne są związane ze środowiskiem życia w okresie dorastania osoby, która w dorosłości zachoruje na schizofrenię. Przyjęcie hipotezy neurorozwojowej implikuje istnienie czynników protekcyjnych, chroniących przez zachorowaniem. W pracy omówiono wybrane zagadnienia środowiskowe stanowiące czynniki ryzyka i czynniki protekcyjne zapadalności na schizofrenię w kontekście ekopsychiatrii. Zamieszkiwanie w środowisku miejskim jest od dekad czynnikiem wskazywanym jako zwiększający ryzyko zachorowania. Współczesne wyniki badań pozwalają na zrozumienie, jak czynnik ten wpływa na rozwój mózgu, ze szczególnym uwzględnieniem zmian objętości istoty szarej w grzbietowo-bocznej korze przedczołowej i przykolankowej przedniej części zakrętu obręczy. Omówiono także wpływ zanieczyszczenia powietrza jako czynnik ryzyka wystąpienia schizofrenii. Narażenie na zanieczyszczenia powietrza zewnętrznego zawierające cząstki stałe i ultradrobne cząstki stałe, gazy, związki organiczne i metale może prowadzić do neurotoksyczności i neuropatologii. Zanieczyszczenia powietrza mogą wpływać na komórki mózgu poprzez wywoływanie stanu zapalnego lub stresu oksydacyjnego. Z drugiej strony sugeruje się, że większy kontakt z terenami zielonymi obniża zapadalność na schizofrenię. Wyniki niektórych badań wskazują, że istnieje zależność dawka–reakcja pomiędzy wielkością przestrzeni zielonej w okresie dzieciństwa a obniżonym ryzykiem późniejszego rozwoju schizofrenii. Przedstawiony tu przegląd wybranych publikacji wskazuje, że w okresie od dzieciństwa aż po wiek dorosły środowisko dorastania ma wpływ na ryzyko zachorowania na schizofrenię. Środowisko zmienione pod wpływem działalności człowieka (urbanizacja) i charakteryzujące się wysokim

stopniem zanieczyszczenia substancjami chemicznymi (toksyny, zanieczyszczenie powietrza, smog) stanowi czynnik ryzyka zachorowania na schizofrenię. Do czynników protekcyjnych należy natomiast bezpośredni kontakt ze środowiskiem naturalnym od dzieciństwa, przez okres dojrzewania, do dorosłości.

Słowa kluczowe: schizofrenia, zapadalność, czynniki ryzyka, teoria neurorozwojowa, zanieczyszczenia powietrza, urbanizacja, naturalne środowisko

For decades, schizophrenia (SCZ) has been classified as an endogenous psychosis and its aetiology remained unknown. As pointed out by Beer (1996), Kraepelin has distinguished between two endogenous psychoses, namely SCZ and cyclothymia (manic-depressive insanity). The aetiology of SCZ has aroused the interest of researchers investigating this disease. The process of describing SCZ risk factors began in the 1980s and 1990s. Although the aetiology of this mental health problem, as a heterogeneous condition, remained unknown, researchers began to describe risk factors. It was also during this time that the neurodevelopmental theory of SCZ was formulated (Murray and Lewis, 1987; Weinberger, 1986). This was a major breakthrough in understanding the disease, as for the first time science had evidence to suggest the existence of factors contributing to the development of SCZ, which made it more rooted in reality and less mysterious. The risk factors described at that time included, among other things, environmental influences.

Authors investigating risk factors of SCZ stressed that a high proportion of liability to this disorder is under genetic control (McDonald and Murray, 2000). It was pointed out that perinatal complications, which are more of a biological factor, increase the risk of SCZ (McDonald and Murray, 2000). In the context of the neurodevelopmental theory of the disease, it was shown that neurodevelopmental deviance is indicated by neurological dysfunction, social, behavioural and cognitive deficits during childhood. However, several studies concluded that many of these SCZ risk factors are environmental influences (environmental risk factors) (Geddes and Lawrie, 1995; Janoutová et al., 2016; Scherr et al., 2012).

Janoutová et al. (2016) emphasised that the consideration of the impact of environmental risk factors in etiopathogenetic studies has put the environment in the forefront of research on the incidence of SCZ. According to these authors, such environmental factors as urbanicity, migration, cannabis use, childhood traumas, infectious agents, and psychosocial influences have been associated with the risk of developing SCZ. Environmental factors that can lead to the onset of the disorder include, for example, being born in the winter months (Bembenek, 2005; Escott-Price et al., 2019; Tramer, 1929) or living in an urban environment (Pedersen and Mortensen, 2001; Vassos et al., 2012). Not all of these factors are relevant to the subject of this paper, which aims to present three selected issues from this long list of environmental risk factors of SCZ.

Nowadays, research points to the role of factors related to the living environment during the developmental period in the development of SCZ in adulthood. In the context of studies on SCZ risk factors outlined above, this paper discusses the risk factors related to the natural vs. urbanised environment where a person who will develop SCZ later in life grows up.

This paper is a narrative review of the available scientific literature with no specified search strategy, based on topic of interest, which is SCZ in the context of upbringing in urban vs. green environments.

THE URBAN BRAIN

According to the neurodevelopmental theory, SCZ is triggered by unfavourable factors acting at different stages of brain development, starting from the foetal period, which affect both its morphology and function. This disruption of brain development during early life underlies the development of psychosis in adulthood (McGrath et al., 2003). The neurodevelopmental hypothesis has been the dominant paradigm for SCZ research over the past decades.

A question emerges whether there is evidence indicating that the brains of individuals raised in urban environments show some specific features. Neurourbanism (Adli et al., 2017) has been proposed as a new scientific discipline spanning neuroscience and urban disciplines including urban planning, architecture, and sociology. Neurourbanism, as an interdisciplinary field of research, focuses on the interdependencies between urbanisation and mental wellbeing with the aim to offer the necessary knowledge and tools to help meet the challenges imposed by urbanisation. It is in this context that Adli et al. (2017) emphasised the role of growing up in an urban environment as a significant risk factor for SCZ.

Based on the same assumption that urban upbringing is a well-established environmental risk factor for SCZ, Haddad et al. (2015) assessed the possible morphological correlate of urban upbringing in human brain. These authors surveyed 110 Germans living in Mannheim and the surrounding areas. The aim of this study was to identify brain structural correlates of urban upbringing as a complex environmental risk factor for SCZ that has been linked to stress exposure in early life. The authors found a difference in the brain structure of individuals growing up in non-urbanised vs. urbanised environments. Their main finding was an inverse relationship between early-life urbanicity and grey matter (GM) volume in the dorsolateral prefrontal cortex (DLPFC) and (in males) the perigenual anterior cingulate cortex (pACC), indicating reduced GM volume in (male)

subjects born and raised in cities. The authors concluded that both the localisation and directionality of the detected main effect of urban upbringing are consistent with the existing literature on the interplay between stress and SCZ. The DLPFC is highly sensitive to stress exposure. Architectural changes of prefrontal dendrites have been repeatedly observed in rodent models exposed to chronic stress, and have been directly linked to stress-induced cognitive deficits. Reduced DLPFC volume has been reported in the context of early environmental adversity in humans. Structural DLPFC alterations are found in schizophrenic patients and certain high-risk individuals. Voxel-based morphometry (VBM) meta-analysis in antipsychotic-naive first-episode patients reported a decrease in GM volume in the right DLPFC. These and previous neuroimaging findings suggest a link between the observed anatomical effects of early urbanicity on DLPFC volume and the risk of SCZ (Haddad et al., 2015).

When considering the reduced volume of the perigenual anterior cingulate cortex (pACC), authors indicate that the cingulate cortex is one of the best supported regions where structural changes are already evident at the onset of SCZ. Volumetric alterations in this region have been associated with both the genetic liability for the illness and environmental stressors, such as urban violence. It has been suggested that these findings extend prior data by highlighting the possibility that the structural integrity of the pACC may be particularly sensitive to the nonlinear cumulative effects of environmental risk factors. Male sex is a well-established risk factor for SCZ, and a higher risk of developing this disease has previously been observed in male individuals born in urban environments.

The conclusion is that urban upbringing may result in anatomical alterations in DLPFC and pACC. Both regions have been implicated in the effects of environmental stress and risk for SCZ. The data emphasise the detrimental interaction of urban upbringing and male sex on brain anatomy, suggesting a complex neural mechanism underlying the relationship between early urbanicity and the risk of SCZ. The described associations of reduced brain volume due to urban upbringing may represent neurodevelopmental changes caused by early urban exposure and increased social stress. The influence of stress in an urban environment does not end once the developmental period is over. Lederbogen et al. (2011) reported functional magnetic resonance imaging findings, indicating that urban upbringing and city living have dissociable impacts on social evaluative stress processing in humans. Their results suggest that current city living is associated with increased amygdala activity, whereas, consistently with publication cited above, urban upbringing affected the perigenual anterior cingulate cortex. These results identify distinct neural mechanisms for an established environmental risk factor and link urban environment to social stress processing, suggesting that brain regions differ in vulnerability to stress as a risk factor across the lifespan.

In the discussion of the results, the authors notice that even if urbanicity effects on the pACC and amygdala were separable, these two structures are functionally closely linked. The pACC is a key regulatory region for amygdala activity in the context of negative affect. Synaptic and neuronal remodelling of the pACC and amygdala have been described in animals exposed to social stressors and amygdala and cingulate volume relate to social network size in humans. Research provided evidence that urban upbringing was associated with reduced connectivity between these structures, whereas current urbanicity had no effect, supporting the impact of early urban exposure on this regulatory circuit.

Lammeyer et al. (2019) investigated the association between urban upbringing and grey matter as well as white matter volume in a sample of healthy subjects. Voxelwise analyses revealed a strong inverse correlation between early life urbanicity and grey matter volume of the bilateral dorsolateral prefrontal cortices (DLPFC), the right inferior parietal lobe (IPL) and the white matter characteristics in the left superior longitudinal fasciculus (SLF). A positive correlation was found for the grey matter volume in the left precuneus. According to the authors, these results represent an altered brain development associated with urban upbringing, which affects not only defined brain regions, but the entire frontoparietal network. Considering the role of DLPFC in stress processing, their findings support the hypothesis of the pathogenetic role of social stress in an urban environment.

In their paper devoted to neurobiological effects of urbanisation, Lambert et al. (2015) emphasised that urban environments represent a divergence from the ancestral habitats of humans and because of that the neurobiological impact of the transition to city living should be carefully examined. Modern species have retained their ancestral brains and, according to these authors, it is important to consider the impact of transitioning to new habitats, such as urban dwellings, over the course of just a few generations. They also emphasised the context of stress exposure in urban environments. On the one hand, such an environment offers better access to important medical, recreational and cultural services and opportunities. On the other hand, urban environments also present disproportionate health challenges. At this point, we return to the topic of stress, since urbanisation in itself can lead to increased rates of trauma exposure due to higher levels of poverty, substance abuse, and crime. Although these authors consider the impact of an urban environment in the context of mood and anxiety disorders, they aptly point to the phenomena underlying the increased impact of stress in an urban setting (Lambert et al., 2015):

- neighbourhoods characterised by greater socioeconomic disadvantage have been consistently found to have higher rates of psychiatric disorders;
- neighbourhoods with higher rates of poverty expose residents to multiple stressors, such as crime, physical and social disorder, and social isolation;

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- neighbourhood disadvantage can affect the level of social organisation and investment in the neighbourhood;
- neighbourhoods with lower levels of social organisation have limited capacity to advocate for health services and resources for individuals with mental health needs, and have weaker social support networks to protect individuals from worsening problems of mood and anxiety;
- neighbourhood disadvantage can affect the resiliency or vulnerability individuals have to stressors and negative life events, which can put them at greater risk of mood and anxiety disorders;
- residents of disadvantaged neighbourhoods are exposed more often to drug activity, which is associated not only with increased drug use, but also increased risk for mental health problems that develop subsequent to drug use.

In the above context, interesting data has been presented by Chinese researchers. If we consider poverty and the impact of stressors such as criminal behaviour, i.e. the aggregate of various types of trauma and poor socioeconomic conditions during childhood, it is possible to expand these considerations to include issues related to reduced intelligence quotient. Premorbid Intelligence Quotient (IQ) deficit, especially when assessed in late adolescence, is a robust risk factor for the onset of SCZ. Numerous studies have confirmed that cognitive deficits are emergent in the early stage of neurodevelopment, including childhood and adolescence, before the onset of SCZ (Xie et al., 2022). Xie et al. (2022) enrolled a total of 400 participants, including 144 patients with first-episode SCZ (FES) and 256 healthy controls (HCs) in their study. Patients with SCZ were recruited among both in- and out-patients of the Psychiatric Department, West China Hospital, Sichuan University. Combining the risk factors for SCZ presented above, the aim of this study was to evaluate the relationship between birthplace or childhood trauma, Intelligence Quotient (IQ), and the occurrence of SCZ (FES).

This study showed that childhood trauma was associated with an elevated risk of SCZ and revealed a rural–urban difference in the IQ of patients with SCZ. Full-Scale IQ (FSIQ) of patients with first-episode SCZ (FES) born in urban areas was lower than that in healthy controls (HCs) born in urban and rural areas. The IQ of patients with FES born in rural areas was lower than that of patients born in urban areas. The authors indicate that 51.46% of the risk of SCZ associated with urban birth was offset by IQ, and 23.12% of the risk of SCZ associated with childhood trauma could be attributable to indirect effects on IQ if these associations were causal.

In summary, some major mental illnesses that are assumed to have a stress-related cause occur more frequently in cities (Haddad et al., 2015). In urban population, the risk of developing mental disorders is 38% higher (39% higher risk for affective disorders, 21% higher risk for anxiety disorders) (Peen et al., 2010). The risk of SCZ is at least two times higher than in people living in rural areas. The dose–response relationship points towards a causal relationship. The more of individual's formative years are spent in an urban environment, the greater is the risk of SCZ in adulthood. Some researchers estimate that up to 30% of the risk of SCZ is attributable to urban upbringing (Adli et al., 2017).

AIR POLLUTION

The importance of the above-described SCZ risk factors was noted already in the last decades of the 20th century. In the early 2000s, papers linking this disorder to exposure to toxic environmental factors appeared (Pedersen et al., 2004; Perrin et al., 2007), including ones highlighting exposure to air pollution and smog (Genc et al., 2012). For example, in one early study from this period, Perrin et al. (2007) observed an elevated risk of SCZ in offspring of parents exposed to a toxic factor called tetrachloroethylene, which is used in dry cleaners. Pedersen et al. (2004) pointed to the role of traffic air pollution. Oberdörster and Utell (2002) first suggested that the brain might be vulnerable to ambient ultrafine particulate matter (UFPM).

Moving on to recent scientific publications, Attademo et al. (2017) conducted a literature review assuming that the risk for psychosis is linked to both genetic and environmental factors, and that the environment can largely influence genetic effects. The authors assumed that air pollution could conceivably be one of the candidate factors to explain this association. They conducted a literature review and identified 13 research reports and 16 review articles, concluding that based on what is known about the pathophysiology of SCZ, it is likely that exposure to xenobiotic heavy metals such as lead and cadmium, constituents of air pollution such as particulate matter (PM) and nitrogen and sulfur oxides, organic solvents, and other constituents of environmental pollution could be component causes of this disease. This data should be viewed in a broader context. It was found that exposure to traffic-related air pollution can lead to neurotoxicity and neuropathology (Costa et al., 2017). Air pollution contains several components, including PM and UFPM, gases, organic compounds, and metals. Traffic-related air pollution, primarily diesel exhaust, is an important source of PM and UFPM. Many studies have shown that exposure to air pollution and traffic-related air pollution may lead to neurotoxicity. In particular, air pollution is considered to be the etiological factor in neurodevelopmental (e.g. autism spectrum disorders) and neurodegenerative (e.g. Alzheimer's disease) disorders. The most prominent effects of air pollution are oxidative stress and neuroinflammation. Exposure to nitrogen dioxide (NO2) and PM during pregnancy and childhood has been linked with poorer neurological and cognitive development (Lertxundi et al., 2015; Sunyer et al., 2015). Newbury et al. (2019) assessed exposure to air pollution in the context of psychotic experiences during adolescence. They relied on the Environmental-Risk Longitudinal Twin Study as a population-based cohort study of 2,232 children born during the

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period from January 1, 1994, through December 4, 1995, in England and Wales and followed up from birth through 18 years of age. This cohort represented the geographic and socioeconomic composition of UK households.

Their results showed that adolescents exposed to high levels of outdoor air pollution were more likely to report psychotic experiences. The levels of pollutants (NO_2, nitrogen oxides – NO_x) statistically explained 60% of the association between urban residency and adolescent psychotic experiences. The authors hypothesised that several mechanisms might account for this association. Air pollutants have potent oxidative effects on lipids and proteins. Subtle abnormalities in brain structure and function have been identified, such as neuroinflammatory markers. These subtle changes together with aberrant prefrontal activity are risk factors for psychotic experiences and they may be caused by air pollution. Thus, air pollution could increase the risk for psychotic experiences by directly influencing the brain and such influences are likely to be cumulative.

They also extend their conclusions to noise pollution (Newbury et al., 2019). The authors believe that the findings therefore implicate road traffic, and by extension, noise pollution. Noise pollution has been linked to stress, sleep disturbance, and cognitive impairments among children and adolescents, which have in turn been associated with subclinical psychotic phenomena.

A study conducted in Swedish children and adolescents (Oudin et al., 2016) included a longitudinal cohort approach covering the entire population under 18 years of age in four major counties in Sweden (roughly half of the Swedish population). It was the first study to use a whole population, and to use nationwide register-based data on dispensed medications as an indicator for mental health. It showed that children and adolescents living in areas with higher levels of air pollution were more likely to have a dispensed medication for a psychiatric disorder during follow-up (HR = 1.09, 95% associated with a 10 μg/m^3 increase in NO_2).

Air pollution can target the CNS through multiple pathways (Attademo et al., 2017). Inflammation and oxidative stress have been suggested as the common underlying mechanisms through which air pollution can induce neurotoxicity, contributing to an elevated risk of neurodevelopmental and neurodegenerative disorders, including SCZ.

Antonsen et al. (2020) conducted a study to answer the question of whether residential exposure to outdoor NO_2, NO_x, PM_{10}, and $PM_{2.5}$ during childhood is linked to an elevated risk for SCZ. Their second question was that if such associations exist, to what degree do they explain some of the differences in urban–rural risks for developing the disorder? Of 230,844 individuals included in this study, 2,189 cohort members were diagnosed with SCZ during follow-up. Their results indicated that the incidence of SCZ was highest among those living in Copenhagen. Children living in the capital and its suburbs also had the highest mean daily exposures to NO_2 and NO_x.

In the whole group, higher levels of NO_2 and NO_x exposure during childhood were associated with subsequent elevated risk of SCZ. People exposed to daily mean NO_2 levels of more than 26.5 μg/m^3 had a 1,62 (95%) times increased risk compared with those exposed to a mean daily concentration of less than 14.5 μg/m^3. The absolute risks of developing SCZ by the age of 37 years when exposed to daily mean NO_2 levels of more than 26.5 μg/m^3 between birth and 10 years were 1.45% (95%) for men and 1.03% for women, whereas when exposed to a mean daily concentration of less than 14.5 μg/m^3, the risk was 0,80% (95%) for men and 0,67% for women. This first population-based study proved that childhood exposure to NO_2 and NO_x is linked with a subsequent elevated risk of SCZ. The authors assumed that some of the urban–rural differences in risk observed might be attributed to urban–rural variability to NO_2 and NO_x exposure.

An even larger population was included in the study by Khan et al. (2019), who published the results of exploratory analyses of 2 independent, very large datasets: 151 million unique individuals, represented in a United States insurance claims dataset, and 1.4 million unique individuals documented in Danish national treatment registers. Environmental Protection Agency (EPA) county-level environmental quality indices (EQIs) in the US and individual-level exposure to air pollution in Denmark were used to assess the association between pollution exposure and the risk of neuropsychiatric disorders. The results of this study clearly indicated a relationship between air pollution and the incidence of mental disorders, although they differed in terms of documenting this relationship with respect to various diagnostic categories.

In the US population, air quality was the strongest predictor for bipolar disorder diagnosis, after the population's ethnic composition. The worst air quality was associated with an approximately 27% increase (95%) in the apparent rate of bipolar disorder. For major depression, a slight increase of 6% in the diagnosis rate (95%) was observed only among the worst air quality regions (Q7). The Denmark analysis suggested that poor air quality during the initial years of an individual's life increases the risk of four psychiatric disorders included in this study (bipolar disorder, SCZ, personality disorder, and major depression). In the US data, a similar trend was found for bipolar disorder (and to some extent for major depression) as that in Denmark, but the signal for SCZ was absent. The authors hypothesised that this difference was caused by the limited resolution of the pollutant exposure estimates for the US data. It is also possible that this difference was partially caused by differences in study design, exposure composition, or country-specific genetic variation. US analysis was focused on association of disease with recent influence of pollution, while Denmark data allowed for evaluating corresponding association with cumulative long-term effect. In summary, this exploratory analysis proved that poor air quality is associated with apparently higher rates of at least bipolar disorder and major

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depression in both US and Danish populations and SCZ in the Danish cohort.

The relationships described here are also present in populations in other parts of the world. Song et al. (2023) published a systematic review and a meta-analysis of papers exploring the association of ambient particulates and gaseous pollutants [NO_2, sulfur dioxide (SO_2), carbon monoxide (CO)] with the risk of SCZ. They identified 17 studies, mainly conducted in Asia, of which 13 were included in the meta-analysis. Increased risk of SCZ was associated with short-term exposure to PM 2.5 μm, PM 2.5–10 μm, PM 10 μm, NO_2, and SO_2. Subgroup analyses showed that females may be more susceptible to SO_2 and NO_2, and that young individuals seem to be more sensitive to PM 2.5 μm and PM 10 μm. Gaseous pollutants presented an immediate risk, while particulates were associated with a delayed risk. This meta-analysis also suggests that short-term exposure to PM and NO_2 may be considered a risk factor of SCZ.

Summing up these results, it can be concluded that air pollution, which is currently one of the world's most serious health problems, contributing to millions of global premature deaths every year (Yang et al., 2023), is also a risk factor for SCZ. It can be assumed that there are many mechanisms underlying the impact of air pollution that increase the risk of SCZ, among which subclinical inflammation and oxidative stress are highlighted. The data supplement our knowledge of the impact of the state of the natural environment on the risk of SCZ. The question then arises whether ecologically favourable environmental conditions can protect against the disease.

CONTACT WITH NATURE

Moving onto the most recent publications on the factors affecting the risk of SCZ, it is worth asking a question whether growing up in an urban environment and exposure to air pollution are risk factors for this disorder, and whether favourable environmental conditions protect against the disease. Based on the neurodevelopmental theory of SCZ, it seems logically justified to presume that if risk factors for the disease have been proven to exist, protective factors must exist as well. This topic can be seen as an example of contemporary trends in psychiatry, i.e. shaping the knowledge and practice of interventions based on contact with nature (nature-based interventions) as ways to improve mental well-being, the quality of life, and reduce stress levels in large populations exposed to severe biological and social stressors (Bloomfield, 2017; Leavell et al., 2019). This strand of research and the introduction of practical solutions grew in importance during the COVID-19 pandemic Murawiec and Tryjanowski, 2020; Randler et al., 2020).

A growing body of scientific literature points out that low exposure to nature, or green space is a risk factor for various mental health outcomes. Higher exposure to green space has been suggested to lower rates of depression, improve children's cognitive development, and reduce neural activity linked to psychiatric disorders. Dose–response relationships between contact with nature and mental health and long-lasting positive outcomes of moving to greener areas suggest causation (Engemann et al., 2019). Poor availability of green space in urbanised areas, where the risk of SCZ is higher, could point to green space as a potentially important protective factor. Green space could mitigate the risk of SCZ by eliminating noise and particle pollution, relieving stress or through other mechanisms (Engemann et al., 2019).

Exposure to green space may influence mental health both psychologically and physiologically. Pathways of this influence could vary for different psychiatric disorders, with green space as a shared risk-decreasing factor. According to Engemann et al. (2019), green space can promote mental health by supporting psychological restoration, encouraging exercise, improving social coherence, decreasing noise and air pollution affecting cognition and brain development, and improving immune functioning.

Engemann et al., 2019 published their study in which they investigated whether access to green space during childhood is associated with the risk of any of the broad range of psychiatric disorders later in life. They combined Danish nationwide population data with individual level green space presence data. The researchers determined the strength and shape of the association between green space and a spectrum of mental health outcomes to clarify whether dose–response relationships can be proved and whether the associations are linear. In the context important for this review, it was also assessed whether the risk of psychiatric disorders is more strongly associated with the presence of green spaces at a specific age during childhood. Green space presence was assessed at the individual level using high-resolution satellite data to calculate the normalised difference vegetation index (NDVI) within a 210 × 210 m square around each person's place of residence (~1 million people) from birth to the age of 10 years.

It was found that high levels of childhood green space are associated with a lower risk of developing any of the spectrum of mental disorders that have their onset in adolescence and persist into adulthood. Their results indicate that the lowest vs the highest exposure to green space is associated with 15 to 55% higher risk, except for intellectual disability and schizoaffective disorder. These protective effects remained after adjusting for other risk factors, including urbanisation, socioeconomic factors, family history of mental illness, and parental age, indicating an independent association with green space.

Relative risk, estimated as incidence rate ratios (IRR), was higher for persons with the lowest NDVI exposure compared with those with the highest levels of NDVI for nearly all psychiatric disorders except for the schizoaffective disorder. The relative risk of developing any psychiatric disorder was related to NDVI in a dose–response relationship across urbanisation levels, with the risk declining with higher doses of green space. The lowest mean NDVI was found for the capital

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centre area, and the strongest association between the relative risk and the lowest decile of green space presence was found for the capital centre region and the weakest association was observed for rural areas (Engemann et al., 2019).

The authors concluded that lower access to green space could be an additional mental health risk factor among vulnerable groups of society. The loss of human–nature interactions presents a risk factor for mental health. It reduces peoples' appreciation of natural environments, creating negative feedback loops. In contrast, positive experiences, such as psychological restoration or social cohesion, can motivate positive ecological behaviours. From the point of view of prophylaxis, increasing urban nature could potentially provide mental health benefits while simultaneously protecting biodiversity and ecosystem services of natural environments.

The same association is found for SCZ. The lowest exposure to green space is correlated with a 1.52-fold increased risk of developing SCZ compared to persons with at the highest level of exposure to green space (Engemann et al., 2018). The same methodology as the one described above for the satellite data from the Landsat programme to quantify green space for Denmark was used to estimate the effect of green space at different ages and within different distances from each person's place of residence on the risk of SCZ. Denmark has a unique opportunity to study the potential association between SCZ and green space since place of residence and health of all citizens are recorded longitudinally in national registers.

The authors demonstrated a dose-response relationship between the magnitude of greenspace during childhood and the risk of later SCZ. This finding was invariant to adjustment for urbanisation and sex. Their analysis highlighted that higher childhood exposure to green space is negatively correlated with the risk of SCZ. The strongest protective association was observed for the earliest childhood years and greenspaces closest to place of residence.

Analogous results were published by researchers from Taiwan (Chang et al., 2019). They used the normalised difference vegetation index (NDVI) as the index of surrounding greenness in their analysis. The NDVI data were extracted using the global moderate-resolution imaging spectroradiometer maintained by the National Aeronautics and Space Administration (NASA) and United States Geological Survey. A total of 5,069 SCZ cases were newly diagnosed during the study period. A significant ($p < 0.05$) negative correlation was found using 2000-m buffer distances (distance of a moderately paced 20-min walk) in the whole Taiwan island, cities, and metropolitan areas. The results of the stratified analysis based on sex and health insurance rate suggested that surrounding greenness has a SCZ-risk reducing effect, regardless of sex or financial status. Therefore, the environmental factors of greenness might play a crucial role in SCZ incidence. A protective effect of greenness exposure was observed, with the strongest protective effect noted in the highest NDVI-rated areas.

According to the neurodevelopmental theory, a significant part of liability to SCZ is under genetic control (McDonald and Murray, 2000). The answer to the question about the association between genetic factors and exposure to a protective factor such as growing up in green spaces is provided by another study (Engemann et al., 2020). Its authors attempted to answer the question of whether this correlation is mediated by genetic liability or whether the two risk factors work additively. The results of this analysis pointed out that the risk of SCZ is additively associated with green space exposure and genetic liability, and provided no support for the environment-gene interaction between NDVI and SCZ. They found that childhood green space and genetic liability for SCZ are uncorrelated. They were independently associated with the risk of SCZ in dose–response relationships: growing up surrounded by more green space is associated with lower risk, whereas having high genetic liability is associated with higher risk. They found no evidence for the interaction between green space and genetic liability for SCZ, indicating that the gene–environment interaction does not increase the risk beyond each risk factor separately (Engemann et al., 2020).

CONCLUSIONS

The studies presented above indicate that the environment in which a person grows up, from childhood through to adulthood, has an impact on the risk of developing SCZ. If this environment is heavily altered by human activity (urbanisation) and, at the same time, characterised by a high degree of chemical contamination (toxins, air pollution, smog), the risk of the disorder increases. Protective factors, on the other hand, include direct contact with the natural environment, such as living in green spaces or visiting such areas in the vicinity of the place where one grows up.

This manuscript focuses only on the preselected environmental risk factors of SCZ, which it was clearly set out in the aims of the paper. Due to the aims of the paper, limited space, and scientific purpose, it was decided that this narrative review does not include literature about other mental disorders or discuss the course or treatment of SCZ.

Jarema (2022) pointed out that when evaluating environmental (ecological) factors and assessing their role in the genesis and course of SCZ, a suggestion of some authors comes to mind that discussing environmental factors in the context of the disease (not only SCZ) resembles a toy referred to as Chinese boxes in Anglo-Saxo literature, and Matryoshka in Russian culture. The idea is that inside a larger doll there is a smaller one which in turn has an even smaller one inside it, and so on. This means that one factor takes precedence over the second and third factors, but it is not possible to consider the role of any of them without looking at the problem holistically, as a set of interrelated factors. Therefore, it is difficult to clearly identify a factor that has a decisive influence on the genesis or course of SCZ, as the environmental factors are interrelated.

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It appears that the research results presented above can confirm this metaphor. Inside the environmental factor of urbanicity, we find a number of factors that fill with concrete content this overriding risk factor. Such factors include, for example, the impact of stress on brain development and exposure to air pollution when brain development processes take place. However, it can also be pointed out that there is more than one set of such "Chinese boxes" as far as risk factors are concerned, and some of them affect this risk independently of each other, yet in an additive manner. It is worth noting the existence of protective factors including contact with nature during the developmental period.

Conflict of interest

The author report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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