The Exposome Paradigm to Understand the Environmental Origins of Mental Disorders

ABSTRACT

There is an active interest in understanding the relationship between mental disorders and modifiable and potentially preventable exposures. However, the complexity of the environment, involving many causal and noncausal pathways, makes research extremely challenging. To tackle these challenges, we have recently proposed the use of the exposome paradigm. The exposome represents the totality of exposures in a lifetime from conception onward. The framework offers a solution to handle the complexity of all “non-genetic” factors. The exposome approach has recently been adopted to construct an exposome score for schizophrenia (ES-SCZ). Findings demonstrate that ES-SCZ can be used for risk stratification, adjusting for cumulative environmental load in statistical testing, and collecting risk enriched cohorts. Increasing data availability will help improve ES-SCZ that can be used in staging models to enhance clinical characterization and outcome forecasting. Although an ES-SCZ already provides several practical benefits for research practice, the exposome paradigm offers much more. Agnostic exposure-wide analyses might be the first step to mapping the exposome of mental disorders. These analyses help distinguish genuine signals from selective reporting and uncover novel risk and resilience factors. The exposome approach will also increase our understanding of the differential impact of the environment on mental health across geographical settings and ethnic communities. We are in the early phases of exposome research in psychiatry; however, if successfully applied, exposome framework is poised to embrace complexity and enable advanced analytical solutions to harness ever-growing data to gain insight into the complex dynamic network of exposures.

Keywords: Exposome, risk, environment, epidemiology, schizophrenia, gene–environment interaction

Introduction

“The contrast between genetic and environmental, between nature and nurture, is not a contrast between fixed and changeable. It is a fallacy of biological determinism to say that if differences are in the genes, no change can occur.” Richard C. Lewontin.

Mental disorders have complex pathoetiology involving genetic and environmental risk factors, as well as their interactions. In the last 20 years, the field of psychiatric genetics has gone through a major restructuring to embrace the complexity of the genome that involve many gene variants of small effect that likely operate on interwoven biological machinery regulated by not a single gene but many genes operating harmoniously in large biological pathways and networks. To understand the molecular genetic background of mental disorders, the Psychiatric Genomics Consortium, adopting the international consortium model, has collected ever-growing samples to take advantage of the ever-advancing high-throughput techniques in genome-wide association studies. Environmental research in psychiatry is as much, if not more, challenging a psychiatric genomics research. To tackle the challenges of investigating environment, Gülöksüz et al. have recently proposed the use of the exposome paradigm—in the same manner with psychiatric genomics research—to better understand the role of the environment in psychiatric disorders.

Gamze Erzin1,2,3
Sinan Gülöksüz2,3,4

1Department of Psychiatry, University of Health Sciences Ankara Dışkapı Training and Research Hospital, Ankara, Turkey
2Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands
3Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA

Corresponding author:
Sinan Gülöksüz silsan.guloksuz@maastrichtuniversity.nl

Received: April 5, 2021
Accepted: April 21, 2021
Available Online Date: June 28, 2021

Cite this article as: Erzin G, Gülöksüz S. The exposome paradigm to understand the environmental origins of mental disorders. Alpha Psychiatry. 2021;22(4):171-176.
In this article, following a brief summary of the role of the environment in mental health outcomes, we first introduce the exposome paradigm and discuss why it might offer a unique perspective to embrace the complexity of the environment underlying psychiatric disorders. We then summarize recent findings from emerging exposome research in psychiatry and finally discuss the future of exposome research.

The Role of Environment in Mental Disorders

In a lifetime, an individual is exposed to a multitude of environmental exposures such as psychological trauma, noise, air pollution, weather conditions, green space that could be predisposing, precipitating, and perpetuating risk factors and protecting resilience factors for mental health outcomes.14,15 There is an active increasing interest in understanding the relationship between mental disorders and environmental exposures as they are modifiable and potentially preventable. However, funding spent on investigating environmental exposures has been lacking considerably. Nevertheless, a growing number of studies have investigated the role of environmental exposures in the pathoetiology of mental disorders. These studies have identified several environmental exposures related to mental health outcomes, such as poor prenatal environment (e.g., poor nutrition, exposure to drugs or toxins, and maternal infections or stress), birth complications, preterm delivery, brain trauma, socioenvironmental exposures (e.g., socioeconomic disadvantages, poverty, urbanicity, immigration, and social isolation), psychological trauma (e.g., parental neglect, physical, emotional, and sexual abuse, as well as exposure to bullying), lack of stimulation, general adversity, drug abuse, and recent stressful life events.8-12

Environmental exposures may operate through various biological pathways and may also induce epigenetic modifications to alter behavioral phenotypes. For instance, environmental exposures, such as cannabis use and childhood adversity, may predispose to schizophrenia by increasing the susceptibility to stress and altering presynaptic dopaminergic functions.13 Each environmental exposure can be a source of stress, which per se plays a role in the development of many mental disorders, from depression to schizophrenia.14,15

The complexity of the environment, involving many causal and noncausal pathways, makes environmental research extremely challenging.16 For instance, suicide risk is increased by environmental factors, such as personal characteristics and adverse life events, whereas suicide risk can be buffered by exposure to green space that is associated with less air pollution,17 which increases the risk of cardiovascular disease, a risk factor for depression per se.18 Some of the environmental exposures increase the risk of mental disorders and influence progression, prognosis, and outcomes. For instance, childhood trauma is associated with an increase in the number of hospitalizations, a decrease in the levels of functioning and quality of life, and predicted higher emotional distress and positive symptoms in patients with schizophrenia.19 Another layer of complexity is the time-specificity of environmental vulnerability, such that exposures during a neurodevelopmental period often have a greater impact. In this respect, cannabis use before the age of 16 years old increases the likelihood of psychosis by 4.6. In contrast, cannabis use after this sensitive period increases the risk by 1.8.20 There exists a dose-dependent relationship between exposures and mental health outcomes: the greater the exposure (in magnitude and duration), the higher the likelihood of mental disorders. The risk of schizophrenia and other psychosis-related outcomes was the highest in the heavy cannabis users compared to the nonusers.21 Furthermore, the majority of environmental exposures are not unique to a specific behavioral phenotype such that cannabis abuse is not associated with psychosis spectrum disorder but also with anxiety, depression, and bipolar disorders, as well as their subtle expressions in the general population.22 In this regard, some evidence suggests that exposure to environmental risk factors increases the connectivity across the symptom network and eventually leads to the development of a clinical syndrome that requires medical care.23-27

The Exposome Paradigm

In 2005, Christopher Wild28 proposed the exposome framework to study the role of the environment (all non-genetic factors from conception onwards) in health and disease processes. Miller and Jones29 refined the exposome framework to include “the aggregate measure of environmental influences and related biological responses throughout the lifefile”. Exposome consists of three overlapping categories: the general external, specific external, and internal.30 The general external domain encompasses factors such as urbanicity, social capital, and stress, whereas the specific external domain includes factors such as diet, smoking, infections, pollutants, and chemical exposures. The internal domain comprises endogenous factors such as gut microbiota, oxidative stress, and metabolism.31

The exposome research paradigm takes into account the complex and dynamic interaction between exposures, and aims to complement the genome.28 The exposome framework offers an agnostic approach to refine findings from previous hypothesis-driven epidemiological studies and aims to lay the groundwork for future hypothesis-testing studies. However, compared with traditional hypothesis-testing epidemiological studies, evaluating the exposome requires much larger sample sizes with enough power to handle the multiplicity and advanced statistical methods and computational power to process multimodal, multilevel, and multidimensional data.32 Furthermore, environmental exposure’s longitudinal and dynamic nature adds an additional layer of complexity for exposome research compared with genomic research.31 To meet these requirements, there is growing investment in exposome-themed research initiatives.33
The Need for Exposome Paradigm in Environmental Research of Mental Disorders

Until recently, environmental research in psychiatry has investigated exposures in isolation by examining the association of a single environmental exposure (e.g., childhood adversity) with a single outcome (e.g., depression). However, accumulating evidence shows that exposures are not phenotype-specific, meaning that exposure such as childhood adversity is associated with many mental disorders, including depression, anxiety, mania, and psychosis (Figure 1A). Furthermore, environmental exposures are not independent entities. There are causal and noncausal associations, as well as interactions between exposures. For instance, cannabis use, an environmental risk factor for psychosis, is associated significantly with other known risk factors for psychosis, such as childhood adversity and urbanicity in the general population (Figure 1B). Childhood adversities and different domains of childhood adversities (e.g., emotional and sexual abuse) are similarly interlinked (Figure 1A). Urbanicity is an environmental exposure defined at the superordinate level and associated with higher rates of other individual-level risk factors for psychosis (e.g., immigrant status, cannabis use, and poor living conditions) that are more frequent in metropolitan areas.

The exposome framework offers a convenient alternative to handle the complexity of all the “non-genetic” factors that compose a dynamic network of exposures and phenotypes. Over the last decade, the exposome paradigm has gained momentum with the availability of large datasets and increased computational power. Environmental research in psychiatry has only recently embraced the exposome paradigm—particularly to construct a cumulative environmental risk load that is the environment equivalent of genetic risk score.

Estimating Cumulative Environmental Risk Score for Mental Disorders

Researchers have so far used various approaches to examine the combined effect of different environmental exposures associated with mental disorders. The majority used a simple total score of environmental risk loading, which was often calculated by simply summing up each environmental factor. However, this approach fails to acknowledge the different magnitude of risk attributable to each exposure. For instance, although obstetric complications, cannabis use, and childhood bullying are all significantly associated with schizophrenia, individual studies and meta-analyses show that the effect size estimates of risk for schizophrenia are different for each exposure.

To overcome the limitation of a simple score that overlooks the varying effect sizes of environmental exposures, previous research employed estimates from meta-analyses to generate a weighted environmental sum score, such as a “polyenvironmental risk score for schizophrenia.” In this study, polyenvironmental risk score for schizophrenia was calculated using a weighted sum score of binary environmental risk factors for schizophrenia that include cannabis abuse, winter-birth, advanced paternal age, urbanicity, obstetric complications, and childhood adversities (i.e., sexual and physical abuse, neglect, and parent death) explained 14% of the variance for transition to psychosis in young relatives of individuals with schizophrenia. Few studies used a similar approach to calculate a meta-analyses-based environmental risk score for schizophrenia, including ordinal and binary categorized set of exposures, with an explained variance of around 4.6% in simulated data and 8.4% in a sample of individuals with first-episode psychosis and healthy controls. By using a weighted sum, a meta-analyses-based environmental risk score...
score appears to provide a better estimate than an environmental sum-score; however, this approach, similar to simple summation, overlooks the interdependency of environmental exposures.

To tackle these challenges, we recently estimated the exposome score for schizophrenia (ES-SCZ) using a predictive modeling approach to estimate and test the ES-SCZ in two independent datasets.\(^\text{42}\) We first applied a multivariable model that takes into account correlation between exposures in a case–control sample to estimate the risk of each exposure for schizophrenia, including cannabis use, winter-birth, hearing impairment, childhood bullying, and five domains of childhood adversities (emotional abuse and neglect, physical abuse and neglect, and sexual abuse). Subsequently, by using these estimates from the training sample, we calculated the weighted ES-SCZ in an independent validation dataset. Our findings showed that the ES-SCZ was more accurate and more sensitive than the environmental sum score and the meta-analyses-based environmental risk score calculated in the same dataset.\(^\text{43}\) Furthermore, the predictive metrics of the environmental risk score calculated using the estimates from the Gaussian Naive Bayes confirmed that the assumption of independent effects in fact led to a reduction in performance.

### Predictive Performance of ES-SCZ

Following up the construction of the ES-SCZ, we have extensively tested its predictive performance in the general population and its utility in clinical samples. In accordance with our initial findings showing a gradient increase of schizophrenia risk as a function of the ES-SCZ, we revealed that ES-SCZ was also associated with the psychosis risk level in the general population.\(^\text{41,44}\) These findings suggest that ES-SCZ can be used to stratify psychosis risk in the general population. Furthermore, ES-SCZ showed a good performance (Area Under Curve = 84) for identifying schizophrenia in the general population.\(^\text{44}\) However, ES-SCZ was not only associated with schizophrenia but also other mental disorders. Although the associations of ES-SCZ with other phenotypes were weaker than that with schizophrenia, these findings show that ES-SCZ would yield only minimal benefit for distinguishing schizophrenia from another mental disorder, such as bipolar disorder.\(^\text{44}\)

In accordance with these findings, we showed that higher ES-SCZ predicted poorer broad mental and physical well-being in a longitudinal population cohort assessed over 9 years in the Netherlands.\(^\text{46}\) Guided by these promising findings from the general population, we tested whether ES-SCZ was associated with global functioning in individuals with schizophrenia.\(^\text{48}\) Our findings that were also replicated in an independent sample revealed that ES-SCZ could be an indicator of poor functioning in individuals with schizophrenia that is independent of the genetic risk score for schizophrenia. We also observed this association between functioning and ES-SCZ in the siblings of individuals with schizophrenia and healthy controls.

Taken together, these findings demonstrate that ES-SCZ can be used for risk stratification, adjusting for cumulative environmental load in statistical comparison models, and collecting samples with increased environmental liability for schizophrenia. Increasing data availability in the future will help improve ES-SCZ that can be integrated with clinical staging models to enhance clinical characterization, outcome forecasting, and clinical management.\(^\text{37}\)

### Exposome Approach to Test Gene–Environment and Environment–Environment Interactions

Recently, Guloksuz et al\(^\text{48}\) showed—for the first time—evidence for an additive interaction between polygenic risk score for schizophrenia and several environmental exposures (cannabis use, childhood bullying, sexual abuse, emotional abuse, and emotional neglect) to increase schizophrenia risk. In light of these findings, a follow-up study for the first time tested the gene–environment interaction using both cumulative scores of genetic and environmental risk for schizophrenia (i.e., PRS-SCZ and ES-SCZ).\(^\text{49}\) The cross-sectional case–control analysis provided further evidence for gene–environment interaction increasing the likelihood of schizophrenia. Furthermore, the analysis of unaffected participants revealed that PRS-SCZ moderated the association between ES-SCZ and subtle psychosis expression, including overall, positive, and negative schizotypy traits—indicative of gene–environment interaction that contributes to psychosis phenotype across the spectrum.\(^\text{49}\) Although there was no gene–environment correlation (i.e., correlation between PRS-SCZ and ES-SCZ) detected in this study, and future studies should measure the degree of gene–environment correlation, as some of these exposures may be partly explained by hereditary predisposition.\(^\text{50}\) For instance, the genetic predisposition for psychosis may be posing a risk for cannabis use and risk for the development of psychosis independently.\(^\text{51}\) However, a recent study applying a within-subject design in a longitudinal cohort showed that cannabis use appears to be causally related to the incidence of attenuated psychotic experiences.\(^\text{52}\) With each individual serving as their control, the within-subject design provides the advantage of eliminating the necessity of considering the confounding by any fixed characteristic that includes genetics.

A recent prospective cohort study of the Dutch general population tested whether the environmental predisposition to schizophrenia, estimated as the ES-SCZ, increased the impact of recent stressful life events as precipitating factors for poor health outcomes at the population level. In accordance with the diathesis-stress theory, both ES-SCZ and stressful life events were independently and interactively associated with poor mental and physical health in the general population, with an environmental predisposition to schizophrenia increasing the stress sensitivity to adverse life events.\(^\text{53}\)

Recently, a series of studies systematically investigated the role of exposome in youth suicidal behavior in the United States. By analyzing data derived from the Philadelphia Neurodevelopmental Cohort, Barzilay et al\(^\text{54}\) dissected the interactive components of exposome underlying suicidal behavior. Findings from this diverse US community population revealed that the association of suicidal behavior with assaultive trauma was moderated by the neighborhood-level socioeconomic status (SES), with youths from higher SES were more prone to the impact of assaultive trauma on suicidal behavior, thereby indicating a stress inoculation in those from low SES.

### Future Directions for Exposome Research in Psychiatry

There is a need to identify and modify environmental risk factors to improve mental well-being at the population level. The exposome paradigm offers a holistic approach to understand the complex, intertwined, and dynamic role of the environment in human health. The exposome approach has recently been adopted in research investigating the role of the environment in mental disorders and...
successfully applied to construct an ES-SCZ that consisted of previously identified exposures, such as cannabis use and childhood adversities. As we outlined, although an aggregate environmental risk score, such as ES-SCZ, already provides several practical benefits for research methodology, the exposome paradigm offers much more to explore the environmental origins of mental health outcomes.

Our understanding of the role of the environment in mental well-being remains limited to a handful of exposures that have been identified in hypothesis-driven candidate exposure studies. In this respect, agnostic exposure-wide analyses might be the first step to mapping the exposome of mental disorders. The exposure-wide analyses help distinguish genuine signals from selective reporting and uncover novel environmental risk and resilience factors. However, the quality and the quantity of the available data have been major limiting factors. In the future, large population cohort studies may provide rich longitudinal data with deep-phenotyping essential to capture the dynamic and interactive attributes of the environment. To increase harmonization and comparability across studies, conventions for measuring exposures should be reconciled and followed in the exposome research of behavioral phenotypes. By embracing the totality of the environment, the exposome approach will also increase our understanding of the differential impact of environmental exposures on mental health across geographical settings and ethnic communities.\textsuperscript{24}

A major challenge in exposome research is the successful mapping of observational findings to mechanistic underpinnings of environmental vulnerability in the biopsychosocial context. Therefore, multidisciplinary teamwork (e.g., psychiatry, neurosciences, epidemiology, and social sciences) is essential for integrating with other multilevel -omics (e.g., genomics, epigenomics) and applying systems biology to disentangle the underlying biological mechanisms. For instance, environmental risk factors may predispose to psychosis by creating susceptibility to stress and disturbing presynaptic dopaminergic functions.\textsuperscript{13} Furthermore, accumulating evidence suggests that inflammation might be a shared final pathway for total exposomic vulnerability to psychosis spectrum disorder,\textsuperscript{21} whereas there might also be biologically distinct mechanisms for individual exposures, such as cannabis.

**Conclusion**

We are still in the early phases of exposome research in psychiatry; however, if successfully applied, exposome framework is poised to embrace complexity and enable advanced analytical solutions to harness ever-growing rich data to gain insight into the complex dynamic network of exposures. Furthermore, a single metric of cumulative environmental vulnerability for mental disorders, such as the ES-SCZ, can help achieve better prediction models. Large, international, collaborative, and multidisciplinary consortiums, akin to the Psychiatric Genomics Consortium, are required to achieve the ambitious goal of unraveling the environmental origins of mental disorders.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**References**

1. Lewontin R. Biology as Ideology: The Doctrine of DNA. House of Anansi Press; 1996.
2. Caspi A, Moffitt TE. Gene–environment interactions in psychiatry; joining forces with neuroscience. *Nat Rev Neurosci*. 2006;7(7):583-590. [CrossRef]
3. Sullivan PF, Agrawal A, Bulik CM, et al. Psychiatric genomics: an update and an agenda. *Am J Psychiatry*. 2018;175(1):15-27. [CrossRef]
4. Gulokszus S, van Os J, Rutten BPF. The exposome paradigm and the complexities of environmental research in psychiatry. *JAMA Psychiatry*. 2018;75(10):985-986. [CrossRef]
5. Dzhambov AM, Markeyev I, Tilot B et al. Pathways linking residential noise and air pollution to mental ill-health in young adults. *Environ Res*. 2018;166:458-465. [CrossRef]
6. Helbich M. Toward dynamic urban environmental exposure assessments in mental health research. *Environ Res*. 2018;161:129-135. [CrossRef]
7. Snijders C, Pries LK, Snamneglia N, et al. Resilience against traumatic stress: current developments and future directions. *Front Psychiatry*. 2018;9:676. [CrossRef]
8. Klomek AB, Sourander A, Elonenmo H. Bullying by peers in childhood and effects on psychopathology, suicidality, and criminality in adulthood. *Lancet Psychiatry*. 2015;2(10):930-941. [CrossRef]
9. Van Os J, Kenis G, Rutten BPF. The environment and schizophrenia. *Nature*. 2010;468(7321):203-212. [CrossRef]
10. Bellasis L, Köhler CA, Stefanis N, et al. Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: an umbrella review of meta-analyses. *Acta Psychiatr Scand*. 2018;137(2):88-97. [CrossRef]
11. Köhler CA, Evangelou E, Stubbs B, et al. Mapping risk factors for depression across the lifespan: an umbrella review of evidence from meta-analyses and Mendelian randomization studies. *J Psychiatr Res*. 2018;103:189-207. [CrossRef]
12. Sideli L, Murray RM, Schimmmenti A, et al. Childood adversity and psychosis: a systematic review of bio-psycho-social mediators and moderators. *Psychol Med*. 2020;50(11):1761-1782. [CrossRef]
13. Howes OD, McCutcheon R, Owen MJ, Murray RM. The role of genes, stress, and dopamine in the development of schizophrenia. * Biol Psychiatry*. 2017;81(1):9-20. [CrossRef]
14. McEwen BS. The brain is the central organ of stress and adaptation. *Neuropsychopharmacology*. 2009;44(7):911-913. [CrossRef]
15. Cohen S, Janicki-Devets D, Miller GE. Psychological stress and disease. *JAMA*. 2007;298(14):1685-1687. [CrossRef]
16. Gulokszus S, Rutten BPF, Pries LK, et al. The complexities of evaluating the exposome in psychiatry: a data-driven illustration of challenges and some propositions for amendments. *Schizophrenia Bull*. 2018;44(6):1175-1179. [CrossRef]
17. Helbich M, De Beurs D, Kwan MP, O’Connor RC, Groenewegen PP. Natural environments and suicide mortality in the Netherlands: a cross-sectional ecological study. *Lancet Planet Health*. 2018;2(3):e134-e139. [CrossRef]
18. Wang R, Xue D, Liu Y, Liu P, Chen H. The relationship between air pollution and depression in China: is neighbourhood social capital protective? *Int J Environ Res Public Health*. 2018;15(6):1160-1173. [CrossRef]
19. Baudin G, Godin Q, Lapnje M, et al. Differential effects of childhood trauma and cannabis use disorders in patients suffering from schizophrenia. *Schizophr Res*. 2016;175(1-3):161-167. [CrossRef]
20. Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ*. 2002;325(7374):1212-1213. [CrossRef]
21. Radhakrishnan R, Wilkinson ST, D’Souza DC. Gone to pot–a review of the association between cannabis and psychosis. Front Psychiatry. 2014;5:54. [CrossRef]

22. Uher R, Zwicker A. Etiology in psychiatry: embracing the reality of polygene-environmental causation of mental illness. World Psychiatry. 2017;16(2):121-129. [CrossRef]

23. Isvoranu AM, Borsboom D, van Os J, Guloksuz S. A network approach to environmental impact in psychotic disorder: brief theoretical framework. Schizophr Bull. 2016;42(4):870-873. [CrossRef]

24. Guloksuz S, van Nierop M, Bak M, et al. Exposure to environmental factors increases connectivity between symptom domains in the psychopathology network. BMC Psychiatry. 2016;16(1):223. [CrossRef]

25. Pries LK, Guloksuz S, Ten Have M, et al. Evidence that environmental and familial risks for psychosis additively impact a multidimensional sub-threshold psychosis syndrome. Schizophr Bull. 2018;44(4):710-719. [CrossRef]

26. Radhakrishnan R, Guloksuz S, Ten Have M, et al. Interaction between environmental and familial affective risk impacts psychosis admixture in states of affective dysregulation. Psychol Med. 2019;49(1):1879-1889. [CrossRef]

27. Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU, van Os J. Evidence that the presence of psychosis in nonpsychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. Psychol Med. 2015;45(1):2389-2401. [CrossRef]

28. Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14(8):1847-1850. [CrossRef]

29. Miller GW, Jones DP. The nature of nurture: refining the definition of the environment. Neurobiol Stress. 2019;56:11-23. [CrossRef]

30. Wild CP. The exposome: from concept to utility. Int J Epidemiol. 2012;41(1):24-32. [CrossRef]

31. Manrai AK, Cui Y, Bushel PR, et al. Informatics and data analytics to support exposome-based discovery for public health. Annu Rev Public Health. 2017;38(1):279-294. [CrossRef]

32. Stingone JA, Buck Louis GM, Nakayama SF, et al. Toward greater implementation of the exposome research paradigm within environmental epidemiology. Annu Rev Public Health. 2017;38(1):315-327. [CrossRef]

33. Plana-Ripoll O, Pedersen CB, McGrath JJ. Urbanicity and risk of schizophrenia—new studies and old hypotheses. JAMA Psychiatry. 2018;75(7):687-688. [CrossRef]

34. Guloksuz S, Pries LK, Delespaul P, et al. Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. World Psychiatry. 2019;18(2):173-182. [CrossRef]

35. Pries LK, Van Os J, Ten Have M, et al. Association of recent stressful life events with mental and physical health in the context of genomic and exposomic liability for schizophrenia. JAMA Psychiatry. 2020;77(12):1296-1304. [CrossRef]

36. Erzin G, Pries LK, Van Os J, et al. Examining the association between exposure to environmental stressors and schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry. 2020;77(2):120-129. [CrossRef]

37. Barzilay R, Moore TM, Calkins ME, et al. Deconstructing the role of the exposome in youth suicidal ideation: trauma, neighborhood environment, developmental and gender effects. Neurobiol Stress. 2021;14:100314. [CrossRef]

38. Burkhard C, Cicek S, Barzilay R, Radhakrishan R, Guloksuz S. Need for ethnic and population diversity in psychosis research. Schizophr Bull. Published online May 5, 2021. doi: 10.1093/schbul/sbab048. [CrossRef]

39. De Graaf R, Ten Have M, van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study–2 (NEMESIS-2): design and methods. Int J Methods Psychiatr Res. 2010;19(3):125-141. [CrossRef]

40. De Graaf R, Ten Have M, van Gool C, van Dorsselaer S. Prevalence of mental disorders and trends from 1996 to 2009. Results from The Netherlands Mental Health Survey and Incidence Study–2. Soc Psychiatry Psychiatr Epidemiol. 2012;47(2):203-213. [CrossRef]