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Environmental Risk and Gene–Environment Relationships in Psychiatric Disorders

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Abstract

Insisting on a distinction between "environmental" and "genetic" risks for psychiatric disorders is imprecise and can be counterproductive. The effect of a genetic variant on a psychiatric outcome may act through environmental pathways. Environmental exposures encountered in life are partly a consequence of how our own heritable traits and predispositions, or those of our parents, interact with our surroundings. This chapter reviews key methods to establish whether an environmental exposure causes an increase in the risk to develop psychopathology or whether it causes psychopathology to relapse. A set of widely studied environmental risks are reviewed for their impact on psychopathology: bereavement, loss, family strife, childhood maltreatment, childhood sexual abuse, trauma, migration and minority stress, exposure to (substance) abuse, sleep, education, and income.

Introduction

The "environment" is a general term and when viewed to be a cause of psychopathology, it evokes different interpretations across disciplines. Sociologists might view racism, sexism, ageism, government policy, or social conventions as possible structural, environmental causes of psychopathology. Health economists might find economic inequality, differences in access to (preventive) care, and market failure in health insurance or health provider markets to be possible environmental causes of psychopathology. Psychologists and psychiatrists might consider parenting, family structure, attachment, stress, and trauma as environmental causes of psychopathology. Developmental biologists and brain scientists might consider hormone levels, vitamins, nutrients, toxins absorbed through exposure or diet to underpin environmental causes of

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psychopathology. None of these perspectives or levels of analysis are wrong; causes at one level (e.g., lead exposure) may mediate causes at another level (e.g., access to safe housing) and require interventions at yet another (e.g., policy changes). It is natural for scientists or practitioners trained in a particular discipline to gravitate to what they have frequently observed or where they feel they can intervene, but an interdisciplinary perspective is necessary to provide clarity and generate valuable avenues for intervention. In fact, innovations in one area (e.g., better preventive psychotherapy) often requires change in another (e.g., policy or funding reform) for those in need to receive effective treatment.

Genetic Risk and Environmental Risk Are Not Mutually Exclusive

It is crucial to recognize that genetic and environmental risk factors are deeply intertwined. If we were to perform a large enough genome-wide association study (GWAS) of the effectiveness of clozapine treatment for schizophrenia, we would almost surely recover an effect of loci in the *CHRNA3/5* (nicotinic receptor) gene cluster. Certain genetic variants in that region predispose people to smoke (more), and because smoking reduces serum levels of clozapine (Tsuda et al. 2014), any allele that predisposes people to smoke will, on average, reduce clozapine treatment success. Whether the effect of variants in the nicotinic receptor gene on clozapine response would be considered a genetic or environmental effect depends on one's perspective. Finding the effect would be highly illuminating if we had no prior knowledge on the role of smoking in clozapine metabolism. If this example is too hypothetical because we do not have very big clozapine GWAS yet, consider that the most significantly associated genetic variant in any lung cancer GWAS that does not control for smoking is in the region of the *CHRNA3/5* gene (nicotinic receptor), clearly the consequence of a causal genetic pathway that acts through the environment.

Even if the mechanisms uncovered by a GWAS reflect a direct biological causal path that plays out entirely within the body or brain, the most direct intervention might be entirely environmental. The most strongly associated genetic variant in the largest clozapine GWAS to date (Pardiñas et al. 2019) is also a lead hit for the coffee consumption GWAS (Coffee and Caffeine Genetics Consortium et al. 2015)—an association that is a likely consequence of the shared metabolism of caffeine and clozapine by the *CYP1A1* and/or *CYP1A2* genes. Regardless of mechanism, the easiest way to improve patient lives directly, given what we have learned from this clozapine GWAS, might involve tighter regulation or monitoring of caffeine (and based on prior evidence nicotine) intake in patient populations (Rajkumar et al. 2013; Tsuda et al. 2014). Genetic associations might reflect environmental associations or highlight paths for environmental interventions. Based on a GWAS of a psychiatric outcome alone, we cannot adjudicate whether a specific significant locus or

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pathway implies a genetic, biological, psychological, or environmental risk for psychiatric disorders or symptoms. In many cases, a pathway involves "all of the above."

It is important to note that genetic associations are not studies of mechanism or etiology; they are a prerequisite for the study of disease mechanism or etiology. GWAS associations allow us to link psychopathology to other complex traits: brain traits, metabolic traits, and molecular traits that confirm or reject specific associations and hypothesized causal relations. While GWAS can help further our understanding of the causes of psychiatric disorders, regardless of whether those causes are understood to be environmental, psychological, or biological, there are certain exogenous (understood to be environmental) risks for psychopathology for which genetic analysis is not the best or obvious answer. As genetic risk and environmental risk are deeply intertwined, it almost always helps to try and account for genetic effects when studying environmental risk of psychopathology.

Risk of *What* Exactly?

A critical nuance that muddles the discourse on the (relative) contribution of environmental and heritable risk for psychopathology is that one must clearly define risk for *what*. Schizophrenia and bipolar disorder are among the most heritable psychiatric disorders, a fact that has been confirmed through multiple orthogonal methods (Golan et al. 2014; Lichtenstein et al. 2009). In the lives of most people diagnosed with schizophrenia or bipolar disorder, they may experience periods of remission as well as relapse, including periods of hospitalization, incarceration, and other adverse outcomes (Jørgensen et al. 2021). The psychological, social, and structural triggers of relapse, hospitalization, or incarceration could be environmentally influenced, even if individual differences in lifetime risk of these occurrences are highly heritable or biological.

The causes of developing schizophrenia need not be the same as the causes of being (un)able to participate in social, economic, and family life with a psychiatric disorder. While these two processes may be correlated and more severely affected patients may generally have significant levels of functional impairment, it would be a categorical mistake to assume that environmental or genetic influence on the disease itself, as well as on its functional consequences, is entirely the same.

Establishing Whether Environmental Risk Factors Are Causal

To determine whether an association with environmental risk is causal (i.e., the environmental factor plays a role in the etiology of the associated outcome rather than simply being correlated with other causal factors) can be challenging. Ideally, we would study the effects of environmental risk factors

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experimentally in randomized controlled trials, but in many cases, ethical and practical considerations prevent experimental manipulation of environmental risks. In the absence of experimental control over environmental risk factors, alternative strategies are needed to ensure that the risk factors are indeed causal and not simply correlated to other causes of psychopathology. It is tempting to fall back on the worn-out meme: "correlation is not causation." Still, it is important to emphasize that not all observational or correlational studies are equal in terms of the evidence they offer for a specific causal relation. We can systematically assess which types of observational study will offer the greatest certainty about the effects of environmental exposures on psychopathology. Here I highlight three specific designs: natural experiments, instrumental variable analyses, and family control analyses. As each of these has potential pitfalls and biases, it is prudent to consider any specific effect of interest across multiple designs when possible. It is also worth noting that all three techniques are sometimes held up as being very close to or fundamentally the same as experimental studies. They are not truly causal experiments, but despite their correlational nature, they enable a more rigorous evaluation of the nature of the exposure and the threats to validity that can offer evidence exceeding a mere correlation.

Natural Experiments

A natural experiment relies on a natural exposure that randomly affects some but not all people in a cohort or study. One critical aspect of a natural experiment that authors need to argue or readers need to be able to confirm is that people randomly encountered the natural exposure. That is, the exposure being studied is uncorrelated to possible other causes of the specific outcome or form of psychopathology of interest. Put in counterfactual terms: by comparing the two groups, we are comparing people that are *interchangeable*; that is, they could have been placed in either group but chance determined their placement in a group. If the exposed group is truly randomly exposed, then measuring the rate of psychopathology in the exposed and unexposed groups after the exposure is sufficient to test whether the exposure effects the risk of psychopathology. If, however, the exposed group is for some reason meaningfully different from the unexposed group, then ideally we would have measures of the rate of psychopathology prior to the exposure and would not need to assume that the exposed and control group are interchangeable, other than their exposure status. Instead, we could assume that *had the exposure not occurred, any prior difference between the exposed and unexposed group would have remained constant*. This assumption is known as the "parallel trends assumption." What does this mean in practice for psychiatric epidemiology?

Consider a fictional experiment that compares a group of Dutch divers on a Pacific diving holiday, who experience a traumatic claustrophobic accident, to the rest of the Dutch population. When analyzing rates of psychopathology

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and use of psycho-pharmaceuticals, pre-exposure risk must be assumed to be identical in both groups. However, people who go on an expensive and somewhat adventurous diving holiday are likely to be wealthier and might have a higher risk tolerance—qualities that could contribute to differences between the divers and other members of the Dutch population. When designing a study or evaluating the work of others, there are two ways to improve this natural experiment. The first involves better matching. One could sample divers who took the same holiday trip the year before as controls; these divers would be well matched for income, risk tolerance, and other unmeasurable or unforeseen confounders. The second concerns the inclusion of pre-exposure measures in both the experimental and control groups. If we have access to pre-exposure measurement of the outcome, we do not need to assume the groups had identical risk prior to exposure but rather that the difference in the groups would have remained constant had the exposure not occurred. Often, researchers cannot access or measure outcomes prior to the natural exposure. In other cases, the parallel trends assumption might fail: even with careful controls in place and a well-selected comparison group, there may be other differences in the groups, had the exposure not occurred. The probability of the parallel trends assumption holding becomes more plausible as the exposed group is better matched to the unexposed group, in terms of known confounders such as age, sex, and prior psychiatric history.

When performed with care, natural experiments provide a powerful way of evaluating the impact of exposures that cannot be ethically or practically manipulated experimentally. Nonetheless, they are limited, because it is difficult to know with certainty whether a natural experiment occurs randomly with respect to all kinds of potential confounders. These confounders may result in differences between the exposed and unexposed group in unknown ways and may bias results.

Instrumental Variables

The use of instrumental variables is another way to examine the causal nature of environmental risk associations. In evaluating treatments or exposures outside the confines of a randomized control study, we are blind to any and all unmeasured influences or processes that could correlate the exposure or risk factor to the outcome. For example, there is concern that the use of selective serotonin reuptake inhibitors (SSRIs) predisposes a person to self-harm or suicide compared to the use of placebo, tricyclic, or other antidepressants (Fergusson et al. 2005; Gunnell et al. 2005). Yet other than through direct comparison in clinical trials (which has been done, but due to the relative rarity of these outcomes require very large sample sizes to offer precise estimates), the relation between being prescribed an antidepressant and self-harm or suicide attempt is deeply confounded by disease severity and numerous other confounders. If there is a source of variation in SSRI prescription (relative to other

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antidepressants) that is unrelated to disease severity or outcome, we could use this as an *instrumental variable*. In instrumental variable regression, we first predict SSRI prescription with the instrumental variable and then regress the outcome of interest (self-harm/suicide) on the *predicted* SSRI use. Key assumptions inherent in this approach include:

1. The instrument influences the outcome *only* through the exposure and not through other related processes.
2. There is no correlation between the instrumental variable and any confounder of the relation between exposure and outcome.
3. The instrument must have a substantial impact on the exposure (SSRI prescription).

Provided these assumptions hold, using an instrumental variable approach can provide unbiased estimates of the causal effects of environmental associations, such as the association of SSRI prescription and self-harm or suicide.

How can this be done in practice? One potential instrument for medication use is found in idiosyncratic personal preferences in the prescription practices of physicians. A British study of approximately 880,000 tricyclic antidepressants (TCA) and SSRI prescriptions (Davies et al. 2013) showed that physicians who in the past were more likely to prescribe an SSRI (relative to TCAs in this study) were more likely to do so in the future, and that while the prescription of an SSRI or a TCA strongly related to the patient characteristics (age, BMI, smoking, prior depression), the long-term prescription preferences of physicians did not relate to these patient characteristics. Thus, physician prescription preference reliably influences whether a person gets prescribed an SSRI or a TCA but appears unrelated to obvious potential confounders of the relation between medication and suicidal behavior. Physician drug preference, therefore, could serve as an instrumental variable that would enable the discernment of drug-specific risks while reducing the confounds induced by patient-specific factors.

While there are numerous other processes that give rise to potential instrumental variables, it is impossible to guarantee or empirically test that an instrumental variable will meet all assumptions and yield unbiased estimates. A specific class of instrumental variables well known to geneticists will be "Mendelian randomization," where a genetic variant serves as an instrumental variable (Sanderson et al. 2022). Critical caveats around the exact interpretation of the effect size arise for instrumental variable analysis, where the instrument, exposure, or outcome is binary—a situation that is fairly common in psychiatric epidemiology.

Family/Sibling Designs

Family designs enable close matching between exposed and unexposed individuals for a range of additional risk factors. The sibling differences model,

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also known as the sibling control model or the family fixed-effect model, is an intuitive model used to study causes of mental illness when unknown or unmeasured confounders are thought to be shared between siblings. By comparing the within-sibling relations between exposure and outcome, we automatically match closely (but not perfectly) the exposed and unexposed groups for parental socioeconomic status, genetic influences, and childhood environment. When twins are used, the exposed and unexposed groups are also matched for prenatal exposures as well as cohort and age effects; monozygotic twins are perfectly matched for genetic risk. We use sibling differences to reframe a research question from "are those who experienced trauma more likely to become depressed" to "are those who experienced *more* trauma than their siblings more likely to become depressed" (Kendler et al. 1999)? In the case of a causal relation between stressful life events and depression, we expect their relationship to persist, even when controlling for anything shared between siblings, as demonstrated by (Kendler et al. 1999).

There are certain limitations in the use of sibling differences models. These models predate modern causal thinking, and interpretation of specific sibling differences models (e.g., stratified Cox proportional hazard models) defy straightforward causal interpretation (Petersen and Lange 2020). The model trades perfect control of shared confounders for risk of bias due to measurement error and confounders specific to a sibling (Frisell 2021). Most applications of sibling difference models consider only linear effects, whereas there are various examples of nonlinear relations in psychiatric epidemiology. I propose that several nonlinear extensions of the sibling model be tested to determine the conditions under which resulting estimates can be interpreted as causal, in a manner consistent with modern causal thinking. Bias due to measurement error or unshared confounders is unavoidable, and other designs have different sources of bias. Thus, triangulation of results across different methods is recommended to safeguard against method-specific biases.

Historically Emphasized and Plausible Environmental Risk Exposures

Several studies have linked environmental factors to mental illness risk. In this section, I review some of these results, both for exposures that plausibly increase the risk of onset of psychiatric disorders and that modify outcomes for people with a history of psychiatric diagnosis. There is a certain risk of bias involved in surveying the scientific literature (whether systematically or casually). Due to limits on what we can measure or the structure of scientific funding, certain topics have historically received more attention and therefore may be overemphasized in a survey or review. Environmental risk for psychopathology is no exception. The survey here inherits these biases, as they are embedded in the underlying literature and thus reflected through the risk factors that

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I have selected. Nonetheless, these risk factors, along with the way in which they were studied, can offer a guide to study further environmental risk factors.

Acute Traumatic Events

The literature on exposure to acute traumatic events as a cause of psychopathology is vast and robust. One notable natural experiment concerns Swedish survivors of the 2004 South East Asian (Christmas Day) tsunami. The nature of this traumatic event was entirely unpredictable. Owing to Sweden's excellent national registries, researchers could link all Swedes that arrived from selected Asian airports into Sweden during the three-week period that followed the tsunami to socioeconomic status and age-matched controls and compare their psychiatric outcomes (Arnberg et al. 2015). Posttraumatic stress disorder and other stress-related diagnoses were strongly elevated among the exposed Swedes (highest aHR = 7.51 for PTSD), and exposure severity was related to outcome severity. The effect was strongest in the first three months after they returned but persisted throughout the entire five-year follow-up period. It is important to note, however, that the researchers did not study differences between exposed and unexposed groups in the change in disease prevalence from before to after exposure (so-called difference in differences analysis), but only considered psychiatric outcomes after exposure.

Bereavement

In the DSM-III and DSM-IV, bereavement was specifically excluded as a cause of major depressive disorder. If a depressive episode resulted from the loss of a loved one, it was implicitly considered a passing state, qualitatively different from other stresses. The situation changed with the publication of the DSM-5. This was a controversial decision. Some argued there was a risk of medicalizing mourning (Frances 2013), while others felt that bereavement should not prevent people with serious morbidity from getting treatment and that obtaining a diagnosis could facilitate proper treatment (Iglewicz et al. 2013). Furthermore, there is evidence that the bereavement period is associated with serious morbidity. For example, the severity of depression symptoms after bereavement is predictive of physical illness in a five-year period following bereavement (Domingue et al. 2021a).

Considering bereavement as a risk factor brings us back to the question: A risk factor for *what*? Some data suggest that manifestations of depression after bereavement do not differ from depression after other stressful life events (e.g., divorce, illness, and job loss as reported by Kendler et al. 2008). However, in a sample of older adults, bereavement raises some but not all symptoms of depression, a finding seemingly consistent with the consequences of grief being different from other forms of depression. It is possible that grief may cause symptoms of depression in a manner inconsistent with depression in

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many or most bereaved individuals, while those who do suffer depression after bereavement are not dissimilar from patients who suffer depression due to other trauma.

Bereavement is also linked to other psychopathologies. For example, in a population-wide study of Danish and Swedish registry data, childhood bereavement (death of a parent) has been associated with a 39% increased risk for schizophrenia (Liang et al. 2016). Some of this risk, however, may be due to a confound of unrecognized parental psychopathology and consequent familial risk factors; if death due to suicide or accident are excluded, the risk increase is only 21% (95% CI13-30%). Others have found children suffering sudden childhood bereavement—due to loss of a father or sibling (N = 6136) compared to loss of a father or sibling due to illness (N = 5719)—is associated with an elevated risk of bipolar disorder and schizophrenia (Clarke et al. 2013), even when excluding suicide as a cause of sudden bereavement.

Finally, a population register-based study in Sweden found that parental bereavement and other trigger events (e.g., traumatic brain injury, self-harm, exposure to violence, unintentional injury, and substance intoxication) are related to an elevated risk of violent crime in the week after the event. For schizophrenia patients, the risk of violent crime is particularly elevated after parental bereavement. Parental loss may affect schizophrenia patients specifically as they may still be socially, emotionally, and economically dependent on the parent (Sariaslan et al. 2020).

Childhood Maltreatment and Sexual Abuse

Various forms of abuse and maltreatment have been linked to psychopathology. A co-twin-controlled study of 1,411 female twins, (Kendler et al. 2000) found that twins who were sexually abused (measured with self and co-twin report) in childhood were at elevated risk for major depressive disorder, generalized anxiety disorder, panic disorder, bulimia, as well as alcohol and drug dependence. The risk of psychopathology was more steeply elevated for those who experienced genital childhood sexual abuse or for whom the abuse involved forced intercourse. Replication in Australian twins discordant for self-reported sexual abuse confirmed elevated depression risk, substance abuse risk, and other adverse outcomes, and generalized the effect to men exposed to sexual abuse in childhood (Nelson et al. 2002). Others have found similar effects of childhood traumatic events (including, but not exclusively, sexual abuse) on the risk for depression, anxiety, somatization, and eating disorders (Brown et al. 2014).

Exposure to Substance Abuse

A large study of high-risk siblings and half-siblings—where one child was adopted out of a family and at least one parent had an alcohol use disorder

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(AUD)—elegantly established the influence of the rearing environment beyond the influence of genetics (Kendler et al. 2021). For siblings from high-risk families, the overall risk of developing AUD was almost fourfold that of the general population, a fact that could be attributed to either genetic or environmental influences. However, siblings adopted out of a family with a parent with AUD had a significantly lower risk of developing AUD [HR sibs = 0.76 (0.65–0.89) and HR half-sibs = 0.77 (0.70–0.84)] than siblings who remained in the birth family, thus establishing a role of the rearing environment on AUD. Risk was reduced less for those adopted into a family with an adoptive parent with AUD than for those adopted into a family without a parent with AUD, further confirming the influence of the rearing environment and extending the finding to include the adoptive environment.

Poverty, Income, and Unemployment

Numerous findings demonstrate associations and causal relationships between economic factors and mental illness. Experimental work in lower- and middle-income countries has demonstrated that when one alleviates monetary poverty in caregivers (or in some cases to youth directly) through cash transfers, the internalization of problems in their children—a strong indicator of causality—is reduced (Zaneva et al. 2022). Importantly, in extreme high-risk situations, the effect of modest cash transfers is insufficient, and the imposition of strict conditions can have negative effects. A quasi-experimental study in the United States showed a benefit of parental income supplementation on offspring mental health in an American Indian population (Costello et al. 2010). Recent register-based studies in Norway, which link parental income to (adopted) childhood outcome, show a modest effect of parental income (Kinge et al. 2021), whereas a Finnish study that leverages sibling discordance for parental income did not find an effect on children's mental health (Sariaslan et al. 2021b). These results suggest a modest or no-effect of income (not poverty) in Scandinavian countries with a well-functioning welfare state. Analysis of Slovenian register data of the entire Slovenian workforce over at least the past decade finds that unemployment is correlated to a steeply heightened risk of suicide and treatment with psychiatric medication. Risk of suicide, but not psychiatric medication use, remained when unemployment was restricted to those cases that had a probable cause unrelated to the individual (i.e., unemployment was caused by a mass lay-off event) (Vodopivec et al. 2021).

For several reasons, the absence of average effects of income on mental health in high income countries with strong social policies should not be considered evidence for the absence of effects of poverty on the individual level in these countries, or the absence of effects in other Western countries with less adequate social policies. First, average effect estimates of income consider the effects of income across the entire distribution and fail to capture nonlinear effects, such as the likelihood that the risk/resource relationship might vary at

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different ends of the income continuum. Relatedly, job loss is buffered by social programs and private savings, which can obscure the relationship between income and risk. Finally, some segments of the population evade adequate capture even in data registers (e.g., the homeless, those with informal or unregistered debts, and those financially deprived by a spouse or parent).

Overall, there is inconclusive evidence on the value of an asset transfer program in middle- and lower-income countries, yet some conditional asset transfer intervention studies register mental health benefits (Lund et al. 2011). In countries that lack a social safety net, there may be a causal relation between poverty and mental health. Finally, the effect of income, employment, and poverty could be mediated by various psychological processes that require additional attention.

Placement in Out-of-Home Care

There are situations where the state needs to step in and help parents or help protect children from their parents. Approximately 5% of children in Western countries are in foster care at some point in their childhood (Fallesen et al. 2014). Placing children in the care of the state has the potential for significant consequences and is so common that it should be the target of sustained empirical study. The long-term consequences of removing a child out of their family home are impossible to study through controlled experiments, because randomly placing children in or out of state care is unethical. Equally, the consequences of foster care cannot be studied through observational studies by simply comparing the outcomes of foster children to the general population, because the causes of family dysfunction that contribute to the risk of placement outside the home are also likely to impact long-term outcomes for the child.

Pioneering work by the economist John Doyle used the fact that case workers in Illinois were assigned to families in an essentially random fashion to examine the effects of foster care. These studies were made possible because these case workers differed substantially in their rate of placing children in foster care as an instrumental variable (Doyle Jr. 2008). Doyle showed that children at the margin of placement who remained at home—those who might have been put in foster care if they had been evaluated by a different case worker—were less likely to be arrested as an adult. Consistent with these findings, nationwide register data analysis of 855,622 children born in Finland between 1986 and 2000 show that children placed in out-of-home care had worse outcomes than their siblings who remained in the home, in terms severe mental illness, anxiety disorder, depression, and personality disorder (Sariaslan et al. 2021a). Further contrasting the type of care for siblings who were both placed in out-of-home care (N = 11,092) revealed that within-sibling pairs, and controlling for a wide array of pre-placement behavioral indicators and risks, the highest risk for depression and serious mental illness occurred in children who received institutional care (vs. foster care) as well as those with the highest

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number of episodes in out-of-home care (Sariaslan et al. 2021a). These studies point to the importance of evaluating the risk of out-of-home-care placement and features of that care (institutional vs. foster care) which can potentially impact adult mental health.

Migration and Minority Stress

Both migration and minority stress contribute environmental risk for mental illness. A widely cited early empirical work by Odegard in 1932 (cited in Cantor-Graae und Selten 2005) established elevated rates of schizophrenia in Norwegian migrants to Minnesota. Similarly, Maltzberg (1936) established that white migrants (controlled for age and urbanicity) to New York state were at 1.4-fold higher risk of being diagnosed with dementia praecox and a 1.2-fold elevated risk for manic depressive psychosis; they were not, however, at elevated risk for alcoholic psychosis. Later work by Maltzberg (1962) established a similar elevated rate of dementia praecox admissions in Black migrants compared to Black native-born New Yorkers. A later meta-analysis (Cantor-Graae and Selten 2005) and Danish population-wide studies (Cantor-Graae et al. 2003) revealed that migrants from a wide variety of countries of origin and with a wide variety of destinations are more frequently diagnosed with schizophrenia. The Danish study also tested but rejected differences in rates of schizophrenia across age upon first residence in Denmark. For those who were born in Denmark to mothers born in Denmark, the study found that those who resided abroad before age 15 had an elevated risk of schizophrenia diagnosis (RR = 1.6, 95% CI 1.25–2.05). In addition, a more steeply elevated risk was observed in migrants from ethnic minority communities compared to migrants from what might be perceived as ethnically the same (evident in higher relative risk for schizophrenia for African, Asian, and Greenlandic migrants than for migrants from other Scandinavian countries). Further evidence of elevated rates for schizophrenia were found in Afro-Caribbean migrants to the U.K. (Van Os et al. 1996), in migrants from Suriname and the Antilles to the Netherlands (Selten et al. 1997), and in migrants to Sweden, with a particularly high-risk in East African and Middle Eastern migrants (Zolkowska et al. 2001). Collectively, these findings suggest that minority stress may further increase the risk conferred by migration.

The leading alternate model to explain the elevated rates of schizophrenia in immigrant communities is selective migration. Those at elevated but subclinical risk for schizophrenia may be more likely to migrate, which would elevate rates of schizophrenia in migrant populations. To test the selective migration hypothesis, Selten et al. (2002) studied Surinamese immigrants to the Netherlands. After Suriname gained independence, over one-third of its population migrated to the Netherlands, which allowed Selten et al. to compare the rate of schizophrenia in Surinamese born immigrants in the Netherlands, using the total Surinamese population prior to migration as a denominator. The

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data showed that the rate of schizophrenia among Surinamese immigrants was higher than among native-born Dutch. A smaller orthogonal test of the selective migration hypothesis compared rates of migration among adopted children who had a biological parent with schizophrenia with adopted children who did not; it found lower migration rates in those with an affected biological parent (Rosenthal et al. 1974). Selective migration does not appear to account for the elevated risk for schizophrenia in migrants and their children.

Prenatal Exposure to Famine

Several studies suggest prenatal exposure to famine as a risk factor for serious mental illness. Two key long-running studies have looked at severe caloric restriction during pregnancy:

- Dutch hunger winter studies, which contrasted women who were exposed to famine in the winter of 1944–1945, when allied offensive and German export embargoes to occupied territories caused severe food shortages in cities in the west portion of the Netherlands.
- Studies of the Chinese Famine from 1959–1961, which was associated with the "great leap forward" set of policies intended to industrialize China.

Contrasting those born in places hardest hit by the famine during the first trimester of pregnancy to those born elsewhere in the Netherlands or immediately before or after this period, researchers identified an elevated risk for schizophrenia in the Dutch national psychiatry register (RR = 2.0, 95% CI = 1.2–3.4) (Hoek et al. 1998). Exposure to the Chinese famine in the first trimester of pregnancy was also associated with an elevated risk for schizophrenia (Xu et al. 2009). A recent comprehensive review also implicates famine as a risk factor for affective and personality disorders as well as for psychotic disorders (Dana et al. 2019).

In the developed world, it is questionable whether famine is still severe or frequent enough to be considered a common or even rare cause of psychopathology. However, most people do not live in the developed world. Even in developed countries, specific vulnerable groups, such as mothers with eating disorders, are observed to give birth to babies with a lower birthweight (Micali et al. 2007). Studying the consequences of malnourishment during pregnancy in the developed world may require nonlinear analysis so that the effects of extreme deprivation can be isolated from other risk factors, as other physical or psychophysical stresses may affect the health of a child. It may also be useful to evaluate the effects of deeply stressful events, such as war (e.g., the London Blitz), in the absence of famine, or stressful personal life events (sudden or violent bereavement during pregnancy) on the risk of psychopathology in the offspring of those affected.

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Sleep

A natural experiment that recurs yearly is the switch to daylight savings time, which moves the sleep midpoint by one hour. Danish registry data shows an 11% (95% CI = 7%–15%) increase in episodes of unipolar depression after wintertime goes into effect (Hansen et al. 2017). This result is corroborated by Mendelian randomization analysis, which reveals that an hour change in sleep midpoint changes depression risk by 23% (95% CI = 6%–33%) (Daghlas et al. 2021). The two studies rely on different designs and different data sets yet reach very similar conclusions. Their consistency illustrates how a fully independent natural experiment and instrumental variable analyses can be leveraged to corroborate a plausible causal relation. Unlike some of the other environmental exposures discussed, sleep can and has been the subject of experimental manipulations. An example is a small, targeted experiment with a more extreme (and qualitatively different) exposure. Researchers compared 25 healthy adults rested at baseline and, after 56 hours of continuous wakefulness, found increased symptoms of anxiety, depression, somatic complaints, and paranoia (Kahn-Greene et al. 2007). Between these extremes and the natural experiments discussed here, there is a wide literature of sleep, restlessness, and insomnia treatment studies. For example, a review of daily diary and momentary assessment studies found that within-person aspects of sleep quality correlate with affect the following day; note also that affect associates with later sleep (Konjarski et al. 2018). These findings point to the widely recognized need to adjust the type of measurement and measurement frequency and interval in studying psychopathology to the timeframe in which the relation between environment and psychopathology occurs.

What About Gene–Environment Interactions?

There is broad interest in the effects of interactions between genes and the environment on psychiatric risk. The study of gene–environment interaction requires both the environmental and genetic risk to be well established (i.e., to be a convincing cause and not just an incidental correlate of psychopathology). Reliably estimating the effects of a gene–environment interaction faces several unique methodological challenges. First, analytic issues (e.g., improper modeling of the distribution of outcome variables) can induce false-positive interactions, even if they do not cause a false-positive main effect (Domingue et al. 2021b). Second, omitting interactions between the environment and the covariates may induce false-positive gene–environment interactions (Keller 2014). Finally, for an interaction to be convincing, we would ideally have tight control over any correlation between genotype and confounders (using, e.g., sibling genetic analysis.), In addition, the environmental exposure would have to be exogenous to ensure it is not potentially correlated with other environments that either confound the analysis or are the true source of interaction (Biroli et

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al. 2022). A rigorous program to study gene–environment interactions would have to contend with these methodological challenges. One study which finds gene by traumatic experience interaction effects on depression risk (Coleman et al. 2020) addresses some but not all of these methodological challenges to validity, and can be viewed as a starting point for future improvements.

Conclusion

This chapter has detailed some experimental design issues inherent in efforts to delineate environmental risk for mental illnesses, reviewed some of the more widely demonstrated examples of environmental risk factors, and briefly considered approaches to gene–environment interactions. There is a massive literature full of carefully performed studies that find specific environmental exposures that relate to risk for psychopathology; some of these (reviewed above) represent a somewhat arbitrary set for which evidence exists from quasi-experimental, instrumental variable, or within-sibling designs. These have been supplemented with experimental designs or intense longitudinal assessments if the nature of the particular environmental exposure was amenable to such studies. Notably, the literature focuses predominantly on mean effects, and one could imagine that the risk of psychopathology increases nonlinearly at the extremes of an exposure. Nonlinear regression and causal inference techniques could help establish whether an exposure has a linear or nonlinear effect on risk and better identify who is at risk. One should avoid confusing effect sizes and estimates of population average causes based on empirical work with the causes and effect sizes of psychopathology in a certain individual. For example, while the magnitude of effect of sleep on psychopathology as assessed in various studies is small, those studies (and their findings) are not necessarily ecologically valid for a mother who has not had an uninterrupted night's sleep for months, due to night feeding and care responsibilities. Future studies aimed at a mechanistic understanding of psychiatric disease risk would do well to consider approaches that take these complexities into account, to move the field forward in a way that is relevant to real-world clinical scenarios.

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