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VIEWPOINT

# Recent findings and future directions for the intersection of genetic and environmental contributions to schizophrenia



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**It is well established that both genetic and environmental factors contribute to risk for schizophrenia (SCZ), and much progress has been made in identifying the specific factors conferring risk. However, the nature and extent of interactions between them has long been a topic of debate. Both the data and methods available to address this have evolved rapidly, enabling new prospects for identifying gene–environment interactions in SCZ. To date, there is limited evidence of strong gene–environment interactions, with environmental factors, molecular genetic risk, and family history simultaneously contributing to risk of SCZ. Still, there are several enduring challenges, some of which can likely be addressed with new tools, methods, and approaches for investigating gene–environment interplay. Consequently, advancements in this field will enhance our capacity to identify individuals most vulnerable to specific environmental exposures, which is pivotal for targeted prevention and intervention.**

## Recent Findings from Molecular Genetics Studies

Family, twin, and adoption studies robustly support the role of genetic factors in schizophrenia (SCZ) (1–4). While early attempts to identify specific genetic markers through candidate gene studies faced challenges in reproducibility, these studies highlighted the importance of properly controlling for multiple testing to reduce the risk of false positives, as well as the need for large samples to detect variants with small effect sizes (5, 6). In the past 15 years, genome-wide association studies (GWAS) and the subsequent cascade of downstream analyses have made great strides in elucidating the genetic foundations of SCZ. Large-scale international collaborations have been instrumental in pooling resources, with the latest study amassing over 76,000 SCZ cases, and this has facilitated comprehensive investigation into the genetic basis of SCZ (7). It is now clear that SCZ is highly polygenic, with risk stemming from the cumulative influence of common and rare variants with small to moderate effect sizes (odds ratios 0.78–1.24) (7), and rare copy-number variants with strong effects (2 to >60x higher risk) (8, 9).

Concomitant with the emergence of genetic associations of high-confidence with SCZ, polygenic risk scores (PRS) were developed to quantify a person's predisposition for a disorder which is attributable to the additive impact of multiple common genetic variants (10). This risk is expressed as a single score, with single nucleotide polymorphisms (SNPs) weighted by their effect sizes from GWAS. SCZ-PRS offers a statistically significant but modest level of prediction and has been used to explore nosology and establish common genetic underpinnings with other psychiatric and somatic disorders (11). PRS methodologies are continually refined to enhance predictive power and improve performance across diverse populations (12, 13).

## Established and Emerging Environmental Risk Factors

The majority of SCZ risk stems from genetic effects but 19%–36% of the risk arises from environmental sources (1, 2). Several environmental risk factors for SCZ have been consistently identified in large-scale epidemiological studies, including cannabis use, pregnancy and birth complications, infections, winter birth, migration, urban upbringing, stressful life events, and childhood adversity (14–17). Air pollution is an emerging risk factor (18) that is complex and typically entwined with social inequality, and there are likely other unexplored environmental and chemical-based risk factors awaiting discovery. While the prevalence of these environmental factors varies across populations, they often disproportionately affect more disadvantaged groups. Some of the identified risk factors are quite common, for instance, childhood adversity (which encompasses parental separation) and adverse perinatal factors each have a population prevalence of ~40% in modern western cohorts (19, 20). Despite the widespread occurrence of environmental risk factors, only a subset of exposed individuals develops SCZ, which strongly suggests differential sensitivity due to underlying genetic predisposition.

Investigations of environmental risk have predominantly involved pursuing individual risk factors in a hypothesis-driven manner, somewhat echoing the early genetic approaches. Just as genetic risk exerts effects through the cumulative impact of multiple genetic factors, it has been proposed that environmental risk may similarly arise from accumulated exposure to a range of adverse environmental factors (21). Over the life course, individuals are subjected to myriad interconnected environmental exposures at different developmental stages, each potentially having protective, neutral, or negative impacts on psychiatric risk. This concept, termed the "exposome," encompasses the entirety of environmental exposures from conception onward (21).

Mirroring PRS approaches, there have been attempts to generate an exposome score weighted by the effect sizes of the environmental factors for SCZ phenotypes (22–25). Unlike genetic studies, which typically require only a single blood sample to derive genetic risk, exposome research requires richly phenotyped, longitudinal, population-based cohorts. While this research is still in early stages, there is optimism that embracing the complexity and dynamic nature of environmental exposures will deliver further elucidation of their collective influence on SCZ.

## Is Gene-Environment Interplay the Missing Link?

Exploring gene-environment interplay, which encompasses both gene-environment correlation (where genotype influences exposure to environmental factors, termed rGE) and gene–environment interaction (where the effect of the genotype depends on the presence of an environmental factor, or vice versa, termed G × E), holds promise for gaining further insight into the etiology of SCZ.

The SNP-based heritability of SCZ identified in GWAS accounts for ~24% of the variance, a stark contrast to the estimates of ~80% from twin studies (2, 4, 7). While rare genetic variation accounts for some of

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the discrepancy, G × E has been theorized to at least partially explain this heritability gap, and this is supported by one recent study (26).

Early G × E studies in SCZ relied on proxies such as family history for genetic risk assessment, or examined single candidate genes, as summarized by earlier reviews (17, 27, 28). These studies encountered similar power issues and biases as candidate gene association studies and often failed to replicate. Genome-wide approaches are considered superior to hypothesis-driven methods for genetic associations but require prohibitively large samples for G × E studies. Therefore, gene prioritization strategies are essential. In one successful example, a genome-wide environment interaction study used a two-stage design to reveal a significant interaction between *in utero* exposure to cytomegalovirus infection and a variant within the *CTNNA3* gene (29). First, the association between the exposure and the complete set of SNPs was assessed, then these prioritized SNPs were examined further to identify interaction effects for the outcome. This variant was not previously linked to SCZ, and this interaction was subsequently replicated (30).

In recent years, a few studies have investigated G × E interactions using PRS as an indicator of genetic liability to SCZ. Most of these studies report independent effects of PRS and environmental exposures and no evidence for multiplicative interactions, including for infections (31), adverse perinatal factors (32, 33), and childhood adversity (34). One study found evidence for an additive interaction effect between SCZ-PRS and childhood adversity on psychosis phenotypes—but it was mediated by a measure of affective dysregulation (35). Even for cannabis use, which demonstrates modest genetic correlations with SCZ (36–38), G × E studies report null interactions. Similarly, for urbanicity, studies support a degree of rGE (39, 40), but null interaction effects for birth in densely populated areas on SCZ risk (41). Still, large-scale genetic studies have rarely considered the impact of variation in environmental risk, highlighting the need for further research in this area.

On the other hand, positive additive interactions have been observed between dichotomized SCZ-PRS and certain environmental factors such as lifetime regular cannabis use and early-life adversities (42). These findings suggest a synergistic effect, indicating that the combined influence of genetic predisposition and environmental exposure exceeds the sum of their individual effects. There was no evidence of interaction effects for winter birth, hearing impairment, or child abuse. Positive additive interactions have also been identified for exposome risk scores and SCZ-PRS for SCZ spectrum disorders (24, 43, 44). Still, there is the need for confirmatory studies in large cohorts and different populations.

Presently, findings from PRS studies do not support the classic G × E (multiplicative) interaction model, whereby genotype and environmental factors only exert effects when both are present. Instead, current evidence suggests that genetic and environmental factors both contribute to risk through either independent or additive effects. However, statistical considerations for detecting and interpreting G × E interactions, such as choice of scale and model selection, are often overlooked. These issues have been extensively discussed, with recommendations for best practice (45, 46). Furthermore, it would be premature to entirely reject G × E hypotheses on the basis of PRS, which capture only a small portion of the expected genetic liability, among other methodological limitations (47, 48).

## Future Focus

The extent to which there is interplay between genetic, familial, and environmental factors in the development of SCZ is still largely unknown. While we now possess a wealth of data on genetic and environmental risk factors, the challenge lies in making connections between them and then translating findings into clinically useful insights.

### Challenges with GWAS and PRS Studies

Although findings from GWAS have provided useful biological insights into SCZ, they have yet to translate into tangible improvements in diagnosis and treatment. Despite their powerful impact on research, PRS have little clinical utility. Moreover, variations between the top and bottom percentiles might be exaggerated due to the case–control design of GWAS, with more modest risk prediction found in other real-world settings such as electronic health records (49). Assortative mating and rGE can also contribute to inflation of GWAS estimates (50). To address this, family-based GWAS designs have been utilized for several disorders by constructing PRS from non-transmitted parental alleles, albeit not yet implemented for SCZ (51). These designs can help identify rare variants and provide less biased estimates of direct genetic effects by reducing confounding from assortative mating and population stratification (51); however, they pose challenges in terms of recruitment of family members of individuals with SCZ, acquiring informed consent, and limited statistical power.

As GWAS sample sizes have increased, so has the proportion of the variance explained by PRS, nevertheless a ceiling effect is impending, whereby further increases in sample size will yield diminishing returns in explanatory power (52). However, these scores may have other useful applications, through correlations with symptoms and clinical features they may prove valuable in distinguishing between psychiatric disorders and optimal treatment approaches (53, 54).

### Expanding the Analytical Toolkit

Although they minimize the multiple testing burden, PRS are likely too broad to be useful for more specific G × E interactions, necessitating more focused approaches and methodological tools. For instance, two-step designs which reduce the initial pool of target SNPs are a resourceful way to circumnavigate the prohibitive multiple testing burden (29, 55, 56). Fine-mapping methods reduce GWAS-derived loci to a smaller set of likely causal variants and can aid prioritization of genes for downstream G × E analyses (7). Modified PRS approaches endeavor to enhance polygenic risk prediction by leveraging correlated phenotypes (57), while others focus on enrichment of genetic variants at the biological pathway level (58).

Beyond genomics, various omics technologies have been applied to examine different aspects of SCZ pathogenesis and may yield further insights about the intermediary paths between genotype and environmental factors (59). These advancements offer novel avenues for capturing genetic risk and biomarkers for downstream application in gene-environment studies.

### Other Sources of Genetic Variation

While recent focus has been on identifying common genetic variants associated with SCZ, rare genetic variants remain relatively unexplored in the context of G × E interactions. Only recently have large-scale collaborations, like the Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium, amassed sufficient sequence data from many studies to identify rare genetic variants with exome-wide significance. The study identified ultra-rare coding variants in 10 genes with strong effect sizes (odds ratios 3–50, $P < 2.14 \times 10^{-6}$) and overlapping findings with the most recent GWAS (60). However, several rare copy-number variations (CNVs), involving deletions or duplications of large segments of DNA, have been identified which can have substantial impact on risk of SCZ. Individuals carrying associated CNVs, such as the 22q11.2 deletion, may be more likely to be exposed to adverse environmental exposures due to the impact on medical, social, and cognitive aspects (61). It has been reported that lifetime stress may influence psychosis risk symptoms in 22q11.2 deletion carriers, suggesting that it may be worth further investigating the role of environmental factors in the expression of psychosis risk among those with CNVs (62). Rare variants could be a promising avenue of exploration in a precision medicine context given that they are a single locus of strong effect, yet their rarity poses methodological challenges in terms of garnering adequate statistical power for scientific investigation. The scarcity of G × E studies using rare variants limits the field's current comprehension of the genetic component of the interaction.

The spotlight on molecular methodologies in human genetics should not overlook the significance of familial phenotypic records in genetic medicine and genetic epidemiology (63). There are several recent and emerging methods for model-based estimates of liability from family records, such as family genetic risk scores (FGRS) (64), the liability threshold on family history (LT-FH) (65), and Pearson-Aitken family genetic risk scores (PA-FGRS) (66). FGRS have already been used to evaluate

diagnostic stability, genetic architecture, and clinical features of several psychiatric disorders (67, 68). Although counterintuitive, PRS and indicators of family history have low correlations and appear to contribute independently to SCZ prediction (66).

### Increasing Ancestral Diversity

The overwhelming majority of molecular genetic studies have been conducted in populations of European ancestry, potentially exacerbating health inequalities and impeding scientific progress (69). Several initiatives are underway to diversify these samples (7, 70), which will provide opportunities to increase our understanding of genetic risk across different environments, cultures, and ancestries.

As with the genetic findings, the bulk of the reliable evidence on environmental risk factors primarily stems from European and North American studies. Nordic registers, documenting numerous medical, social and demographic factors for the entire population from birth, are a rich resource for investigating the impact of environmental risk factors in rare psychiatric disorders and have provided some of the most robust epidemiological estimates (20, 71, 72).

Exploring more diverse settings and countries with greater environmental variability will likely clarify whether there are key cultural differences and aid understanding of true etiological associations. The challenge persists that to comprehensively investigate the genetic and environmental contributions to SCZ requires the rare combination of large, genotyped cohorts with longitudinal assessments of several environmental exposures over the life course.

## Conclusion

There is still much to uncover regarding the interplay between genetic, familial, and environmental factors in SCZ. Undoubtedly, there are additional environmental factors and gene–environment interactions yet to be discovered. Given the high degree of shared genetic and environmental risk among psychiatric disorders, exploring G × E may help to isolate disorder-specific associations and pinpoint mediating or moderating biological pathways. Advancements in genetic and statistical tools will likely accelerate G × E research and maximize the utilization of existing datasets. The prospect of identifying individuals most vulnerable to specific environmental exposures underscores the importance of further exploration, offering opportunities for prevention and intervention.

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