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COMMENTARY

Nature, Nurture, and the Polygenic Risk Score for Schizophrenia

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Technological progress is reshaping the *nature versus nurture* debate of disease causation. Fifty years ago, psychiatrists used to argue over whether schizophrenia was caused by a single gene or some unknown environmental factor. We now know that there exist a range of component causes, or risk factors, for schizophrenia, both genetic and environmental. So, what do we argue about now? Often the relative importance of the 2 sets of factors. The favorite measure of geneticists has been heritability, often quoted as 60%–80% for schizophrenia, but this disregards the evidence that heritability estimates are inaccurate in the presence of gene-environment correlations or interactions.[1]

Then, Genome Wide Association Studies (GWAS) arrived, followed by huge collaborative efforts that examined hundreds of thousands of people, not only for psychiatric and physical illnesses, but also for behavioral traits such as IQ, personality, or physical traits such as height. Psychiatric disorders, like most common noncommunicable disorders, were found to be polygenic, associated with thousands of genetic markers. Although the effect of each marker is small or negligible, an aggregate score constructed as the sum of the weighted effect of all the markers together, the so-called Polygenic Risk Score (PRS), has much higher predictive ability. Two characteristics of PRS have exponentially increased its popularity: (1) its inherent simplicity, being a normally distributed measure that summarizes the total genetic loading and (2) the fact that it builds on large global GWAS of thousands of individuals, which makes it a powerful predictor even in small target samples.[2]

As PRS was first developed and applied in schizophrenia (PRS-Sz), there has been an explosion of studies in the field. The PRS-Sz calculated from the latest Psychiatric Genomic Consortium data[3] explains about 7% of the variance of schizophrenia in the general population, assuming 1% prevalence. This is higher than other psychiatric and most physical disorders, despite the heterogeneity of schizophrenia and the fact that samples included in GWAS are compilations of individuals with different component psychopathologies. Despite the impressive effect size, geneticists have repeatedly acknowledged that PRS is not powerful enough to be useful for screening for psychosis in the general population.[3]

However, researchers have tested different hypotheses in targeted populations. For example, among first-episode psychosis patients, PRS-Sz can differentiate schizophrenia from other psychosis.[4] PRS-Sz has also been applied to predicting the outcome of psychosis with some, but not huge, predictive power[5] and to so-called endophenotypes, eg MRI abnormalities, or event-related potentials.[6] Another interesting use for the PRS has been its application to huge population samples. For example, PRS-Sz has been associated with psychotic-like experiences in the UK Biobank[7] and, more surprisingly, with creativity in Iceland.[8]

The PRS can be used to study the interplay of genes and environment. First, it can be used to examine whether environmental factors are independent or are themselves subject to genetic influence by the outcome. In some cases, research has shown that whether an individual is exposed to a risk factor eg cannabis use or urbanicity[9] is partly under the influence of the genetic liability to schizophrenia. One can also address the question of how genes and environment act together to produce disease. It could be that the effects of the two add up to increase risk or that some individuals are genetically susceptible to the effect of the environmental factor. Evidence so far tends to favor simple additive models, but much larger samples will be needed to examine this question properly.

It is in this context that Marsman et al (2020), in this issue, return to the old question of the relative contribution of genetic and environmental risk factor(s) to the variance in mental health in a population-based study. This is a novel question as most studies focus on selected case-control and not population samples. The sample used (NEMESIS-2) was followed up for 9 years with 2380 subjects seen on all 4 occasions. General mental health was assessed using the Short-Form-36 Health Survey (SF-36), an easily administered scale of quality-of-life measures. The mental health dimension comprised items related to emotional health, role limitations due to emotional problems, social functioning, and vitality. Family history was measured as were socioeconomic status, childhood trauma, urbanicity, cannabis use, and life events.

All the predictors together accounted for 17% of the variance in mental health; of this proportion, 5% was explained by age and sex, 30% by social circumstances, 16% by bodily pain, 22% by environmental risk factors, 24% by family history, and just 3% by PRS-Sz. Among the environmental exposures, childhood trauma had the greatest effect, which is perhaps not surprising given that it increases risk across most psychiatric disorders. On the other hand, urbanicity and cannabis were not found to explain significant variance; the former is surprising, given the effect of urbanicity risk across psychiatric disorders[10]; the later probably reflects the fact that cannabis has been consistently shown to increase risk of psychosis but evidence for a more general effect on psychiatric disorders is lacking.

In short, the contribution of PRS-Sz to the variance of mental health was very small, but the outcome was a measure of well-being rather than severe mental illness. The variance explained (0.4%) is not dissimilar to studies employing PRS-Sz to predict phenotypes other than case-control status and reflects the lower power in such analyses. Arguably, any transdiagnostic prediction by PRS-Sz is noteworthy. It is interesting that family history performed so much better than the PRS-Sz, but of course, it includes intrafamilial environmental effects and genetic effects. Also, as the family history measure included a variety of disorders, not only schizophrenia, it was more relevant to the outcome studied.

Furthermore, it is difficult to make a head to head comparison of the relative contribution of risk factors. The estimated main effects of predictors in a model depend on the covariates used and unmeasured factors, such as unmodeled interaction effects. For example, we know that Huntingdon's disease is 100% genetic (people with >40 CAG repeats will develop it with full penetrance if they live long enough). However, if in a sample of relatives of patients with Huntington's disease, a regression model uses age and number of CAG repeats as predictors of the disease, age will explain a considerable proportion of the variance. This does not make the disease less genetic.

The authors rightly conclude that socioenvironmental factors explained the bulk of the variance of mental health, with PRS-Sz making only a small contribution. This is an important finding because it highlights the limitations of the uncritical applications of PRS-Sz in any phenotypes. Does this make PRS-Sz obsolete? No, but realistic hypotheses need to be developed. Accepting that PRS lack impact in analyses focusing on prediction in epidemiological setting, it remains a useful tool for the biological validation of psychopathology constructs and for making etiological inferences. As we are born with our genes, which predate the disease onset or any socioenvironmental risk, any associations or mediation effects can only be one directional.

These are early days, and PRSs are constantly being refined and gaining statistical power. PRSs represent the crude summing of all variants influencing risk of the phenotype in question. It may be that within this single measure, gene subsets based on specific biological processes (eg neurotransmitter systems) or PRS for specific pathology rather than clinical syndromes can be calculated and applied to the study of gene-environment interaction. For example, would one expect the same genetic pathway to make an individual more susceptible to schizophrenia when exposed to obstetric complications, child abuse, or drug abuse? It should soon be possible to answer such questions.

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Conflict of Interest

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