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Premature Mortality and Schizophrenia—The Need to Heal Right From the Start

To the Editor Using a retrospective Medicaid database, Olfson et al[1] reported an alarming 3.5-fold increased and growing mortality risk in people with schizophrenia. Standardized mortality ratios were particularly high for cardiovascular illness and smoking- and substance use–related mortality causes. One acknowledged relevant limitation of this study, and all database studies, was lacking information on established risk factors. While the assessment of diet and exercise is not part of usual care, data on smoking, weight, and glucose and lipid levels are available, collected (albeit still far too incompletely) and available in patient medical records. There is an enormous need and opportunity to include this crucial information as part of insurance and other large databases.

This article[1] builds on the international recording of the premature loss of life in people with schizophrenia, much of it preventable and termed a "scandal of premature mortality that contravenes international conventions for the 'right to health.'"[2] A key finding in the article from Olfson et al[1] was that deaths due to diabetes and cardiovascular disease particularly disadvantaged younger people.[1] Cardiovascular disease contributed one-third of the mortality.[1] This finding underscores that much of the preventable mortality gap occurs early in life.

Recognizing the early phase of psychosis as a critical period for acquiring and preventing cardiometabolic risk, an international working party of psychiatrists, physicians, allied health workers, and people with lived experience launched the Healthy Active Lives Declaration in 2014, mandating physical health care standards to proactively address these risks.[3] The declaration defined specific measurable 5-year targets, with systematic monitoring of weight, cardiometabolic risk factors, and smoking and specific early intervention strategies that can succeed (http://www.iphys.org.au).[4]

This declaration established a vision of physical health in severe mental illness and set standards for cardiometabolic disease prevention, just as the St Vincent's Declaration benchmarked diabetes care 20 years ago. What if the sobering findings of Olfson et al[1] had instead applied to people with diabetes? It is unconscionable that we would ignore opportunities to prevent cardiovascular disease and diabetic complications. Mental health starts with physical health.[5] The Olfson et al study[1] should be a loud wake-up call for psychiatrists, general practitioners, and physicians to work together to integrate body and mind from the start of psychosis and its treatment. People with severe mental illness and their families should expect physical health monitoring and preventive interventions as routine care right from the start.

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Genomic Approaches to Phenotype Prediction

To the Editor Methodological considerations raised by Lord and Veenstra-VanderWeele[1] regarding genotype-first approaches to phenotype research are appreciated. In their editorial focusing on autism spectrum disorder, the authors described the importance of considering phenotypic confounds. This letter expands on these considerations with discussion of novel methods increasingly used for predicting and classifying psychiatric phenotypes from genetic data. These developing methods may be further useful in resolving confounds.

There are several approaches to using common genetic variants in prediction. Polygenic risk scores, derived from genome-wide association regression weights, are frequently used to predict case status or quantitative complex traits. Similar methods use the other side of the genome-wide association *P* value distribution to derive scores associated with resistance to disorder. In addition, pathway-based polygenic scoring methods are currently being tested by our group to examine the aggregated weights of thousands of variants within only the molecular pathways demonstrated to be enriched in disorders (specifically, gaussian clustering on pathway scores enriched in cases and contrasting proportions of subtypes within leaves of a regression tree, both accounting for ancestry and sex).[2] Molecular pathway-based scores can reduce the genomic information to a computationally reasonable size, while increasing signal-to-noise ratio.

While these methods have promise, it is important to be realistic about what these analyses might uncover—in many studies, we see common variant heritability estimates plummet in comparison with those from twin studies. However, Lord and Veenstra-VanderWeele[1] point out that the phenotype-first approach to complex, low base rate disorders is often impractical. In these cases, scoring may be useful in at least 2 ways: individual cases can be assigned to a genetic subgroup based on pathway scores and subtypes can then be differentiated phenotypically (A.R.D., D. E. Adkins, PhD, A. C. Edwards, PhD, M. C. Neale, PhD, B. P. Riley, PhD, K. S. Kendler, MD, A. H. Fanous, MD, PhD, and S. A. Bacanu, PhD; unpublished data; December 2015). Additionally, although exploratory methods should be used with caution, phenotypic network analyses can be examined across genetic subtypes.

Finally, genetic profile scores can be examined with respect to the entire phenome. Thus, genetic risk across mental health conditions can be used for phenotypically savvy research on quantitative clinical and outcome variables. One example is a report by Krapohl and colleagues,[3] and another could relate to Lord and Veenstra-VanderWeele's discussion of multiple, quantitative phenotypes, such that polygenic risk for autism spectrum disorder within a deletion subtype could be used to predict any number of networks across the phenome. Duplication and deletion information can also be used to subtype, and to maximize the genetic risk accounted for, while simultaneously accounting for ancestry and sex.

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