Schizophrenia Bulletin vol. 34 no. 2 pp. 247–248, 2008
doi:10.1093/schbul/sbm133
Advance Access publication on November 28, 2007

Dissecting the Heterogeneity of Schizophrenia Outcomes

John McGrath[1-3]

[2]Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, Queensland 4076, Australia; [3]Queensland Brain Institute and Department of Psychiatry, University of Queensland, Brisbane, Australia

Key words: schizophrenia/outcome/epidemiology

Goethe believed that data are the natural enemy of hypotheses. As new data accumulate, only a few lucky hypotheses survive the fresh empirical onslaught. Over time, most hypotheses eventually need amendment or outright rejection. Schizophrenia epidemiology has been a particularly fertile field in recent years, with new data leading to the revision of several long-standing dogmatic beliefs.[1–3] The target article by Cohen et al[4] questions another of the oft-repeated tenets of schizophrenia epidemiology. After close inspection of the schizophrenia outcome studies based in low- and middle-income countries, the authors reject the notion that outcomes in these sites are superior to comparable published data from high-income countries.[5] It is curious that the hypothesis related to economic status captured the attention of the research community at the expense of the more general finding to emerge from the World Health Organization study, which was that clinical outcomes varied widely within and between sites, regardless of economic status.[6] The review by Cohen et al[4] reminds us that crude ecological variables related to national economic status do not seem to help untangle this heterogeneity.

In recent decades, there has been a substantial research effort focused on the identification of the *onset* of psychotic disorders.[7,8] However, we still struggle to understand the *offset* of schizophrenia.[9] Categorical outcome measures (eg, recovered vs persistent illness) are not readily operationalized for chronic disorders such as schizophrenia. Dimensional symptom outcomes (eg, positive or negative symptoms) and more ''downstream'' measures of disability (eg, employment, social functioning) tend to fluctuate over time and show divergent trajectories. Compared with measuring incidence, prevalence, and mortality, the assessment of clinical outcomes in schizophrenia is much more of a challenge.[10,11]

Apart from the multidimensional nature of outcome measures, there are methodological concerns about how best to compare results from studies with different intake criteria and different durations of follow-up. With respect to intake criteria, outcome studies can be based on (a) incident cases or (b) mixed incident and prevalent cases. Prevalent cases are enriched with those with chronic illness and depleted of those who have died. The target article draws attention to the potential for differential between-site mortality to bias assessments of clinical outcomes. A recent systematic review of mortality in schizophrenia found prominent variation between sites; however, there was no significant difference in standardized mortality ratios between sites when sorted by economic status.[12] While thought provoking, these and related ecological analyses based on economic status[13] should be treated cautiously because of the relative lack of data from low- vs higher income nations.

With respect to duration of follow-up, studies can measure outcome at widely different time intervals (eg, 5 vs 25 years). Outcomes measures are usually provided as ''percent recovered'' or proportions describing other outcome-related measures. However, is it valid to compare ''proportions recovered'' between studies with different durations of follow-up? Solutions such as annualized remission rates are also suboptimal (eg, if 20% of a sample achieves remission criteria at 10-year follow-up, the annualized remission rate = 2%). This derived measure assumes that the chance of recovery is evenly distributed over time, which is an unlikely scenario for any disease.

Because we do not expect that schizophrenia outcomes will obediently map on to geopolitical boundaries, within-nation differences should also be studied alongside between-nation differences. Sites can compare the relative influence of factors known to influence the chance of remission (eg, sex, age of onset, duration of treated and untreated psychosis) and also explore the impact of risk factors such as urban birth and/or residence, migrant status, and neighborhood-level variables related to social capital. The contours of schizophrenia epidemiology within nations may be more informative than previously appreciated.[3]

The take-home message from the target article is that clinical outcomes in schizophrenia are heterogeneous (as

[1]To whom correspondence should be addressed; tel: 61-7-3271-8694, fax: 61-7-3271-8698, e-mail: john_mcgrath@qcmhr.uq.edu.au.

is the case for incidence,[14] prevalence,[9] and mortality[12]). The heterogeneity in these estimates mirrors the marked clinical and neurobiological heterogeneity of the disorder.[15] Cultural and socioeconomic factors would contribute to the variability in outcomes via many different pathways. Less widely canvased, underlying genetic differences between groups may also contribute to differences in both the risk of schizophrenia and the clinical outcome. The HapMap project has demonstrated that our species shows between-group genetic variations, and while there is substantial variation within geographically defined populations, there remains between-group differences that reflect ancient geographical origin.[16] Some of these variations have been linked to disease susceptibility.[17,18] With respect to clinical outcomes, evidence from other chronic disorders suggests that the genetic factors that predict recovery from an illness may differ from those genetic factors that increase susceptibility to that disorder.[19,20] This may also be the case for clinical outcomes in schizophrenia.

Finally, the article by Cohen et al[4] is timely. Understanding the interactions between incidence, prevalence, mortality, and remission underpin the calculation of the Disability-Adjusted Life Year, a metric increasingly used to prioritize health service delivery.[21] Detailed population-based estimates for clinical outcomes will be required for the next Global Burden of Disease study.[22,23] The target article by Cohen et al[4] provides a useful resource for this exercise and should galvanize more empirical research in the field of schizophrenia outcomes.

References

1. McGrath JJ. Myths and plain truths about schizophrenia epidemiology–the NAPE lecture 2004. *Acta Psychiatr Scand*. 2005;111:4–11.
2. McGrath JJ. Variations in the incidence of schizophrenia: data versus dogma. *Schizophr Bull*. 2006;32:195–197.
3. McGrath JJ. The surprisingly rich contours of schizophrenia epidemiology. *Arch Gen Psychiatry*. 2007;64:14–16.
4. Cohen A, Patel V, Thara R, Gureje O. Questioning an axiom: better prognosis for schizophrenia in the developing world? *Schizophr Bull*. September 28, 2007; doi:10.1093/schbul/sbm105.
5. Hopper K, Wanderling J. Revisiting the developed versus developing country distinction in course and outcome in schizophrenia: results from ISoS, the WHO collaborative followup project. International Study of Schizophrenia. *Schizophr Bull*. 2000;26:835–846.
6. Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol Med Monogr Suppl*. 1992;20:1–97.
7. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull*. 1996;22:353–370.
8. McGlashan TH. Early detection and intervention of schizophrenia: rationale and research. *Br J Psychiatry Suppl*. 1998;172:3–6.
9. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005;2:e141.
10. Hafner H, An der Heiden W. Course and outcome of schizophrenia. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia*. Cambridge, UK: Cambridge University Press; 2003:101–141.
11. Andreasen NC, Carpenter WT Jr., Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162:441–449.
12. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64:1123–1131.
13. Saha S, Welham J, Chant D, McGrath J. Incidence of schizophrenia does not vary with economic status of the country: evidence from a systematic review. *Soc Psychiatry Psychiatr Epidemiol*. 2006;41:338–340.
14. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med*. 2004;2:13.
15. Tamminga CA, Holcomb HH. Phenotype of schizophrenia: a review and formulation. *Mol Psychiatry*. 2005;10:27–39.
16. Tishkoff SA, Kidd KK. Implications of biogeography of human populations for 'race' and medicine. *Nat Genet*. 2004;36:(suppl):S21–S27.
17. Balaresque PL, Ballereau SJ, Jobling MA. Challenges in human genetic diversity: demographic history and adaptation. *Hum Mol Genet*. 2007;16(Spec No. 2):R134–R139.
18. McGrath JJ. The romance of balancing selection versus the sober alternatives: let the data rule (commentary on Keller and Miller). *Behav Brain Sci*. 2006;29:417–418.
19. Spitz MR, Wu X, Mills G. Integrative epidemiology: from risk assessment to outcome prediction. *J Clin Oncol*. 2005;23:267–275.
20. Waters RJ, Nicoll JA. Genetic influences on outcome following acute neurological insults. *Curr Opin Crit Care*. 2005;11:105–110.
21. Murray CJ, Lopez AD. *The Global Burden of Disease*. Boston, Mass: Harvard School of Public Health; 1996.
22. Lopez AD. The evolution of the Global Burden of Disease framework for disease, injury and risk factor quantification: developing the evidence base for national, regional and global public health action. *Global Health*. 2005;1:5.
23. Murray CJ, Lopez AD, Black R, et al. Global Burden of Disease 2005: call for collaborators. *Lancet*. 2007;370:109–110.