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Commentary on Bai et al

Families, health-registers, and biobanks – making the unmeasurable measurable.

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‘Measure what is measurable – make measurable what is not so’. Galileo Galilei

Galileo’s recommendation on how to conduct scientific research could not be more concise, nor more accurate. To advance knowledge, we should observe the natural world with the best available tools, and for things that we cannot currently measure, fill that gap by making better tools and keep measuring. With his early telescopes Galileo was able to sketch the irregularities on the surface of the moon, and subsequently he built more powerful telescopes to observe distant objects (e.g. the rings of Saturn, the moons of Jupiter). When it comes to understanding the causes and consequences of mental disorders, we have many different telescope-like instruments in our tool kit. One such tool is epidemiology, which describes the distribution of disorders and risk factors across time and space. With respect to psychiatric research, epidemiology can observe frequency measures (e.g. incidence, prevalence, recovery, mortality) and explore candidate risk factors (both genetic, and nongenetic) for mental disorders. The most powerful ‘telescopes’ of psychiatric epidemiology are population-based surveys and health registers. The target paper of this commentary (1) is based on the remarkable Swedish health registers. The researchers have improved the optics of their research by cross-linking the population-based registers with information on family linkages. With this extra lens, they were able to explore curious and yet-to-be understood features of Autism Spectrum Disorder (ASD).

Autism spectrum disorder (ASD), like schizophrenia and attention deficit hyperactivity disorder, is more common in men than in women. It remains unclear why this is so. Generally, it has been postulated that the developing male brain is less resilient, and thus given the same genetic liability for developing ASD, men are more likely to express neurodevelopmental outcomes such as ASD. The flip side of this hypothesis is that women are more resilient, and while they may inherit an equal load of (autosomal) risk variants from their parents, compared to men they are less likely to express the ASD phenotype. This hypothesis is testable — national health registers could be used to identify people who were diagnosed with ASD, and by linking these individuals across family pedigrees, researchers can start to focus on the transmission of ASD via both affected and unaffected men and women across generations.

In an article in this volume, Bai et al. explored this hypothesis — they compared the ASD risk in offspring to women with an ASD affected sibling to that of the offspring of men with an ASD affected sibling. If the male-to-female sex ratio in ASD (typically 3 or 4 to 1) can be attributed to female resilience in the face of genetic risk factors, then the mothers in this study should (on average) carry
over considerably higher genetic load and associated ASD risk compared to the fathers. The risk of ASD in the offspring of women with an affected sibling was 1.88 (95% Confidence Intervals 1.54-2.26). The comparable estimate in men with an affected sibling was 1.44 (95% CIs 1.05-1.86). Thus, a fairly small difference with overlapping confidence intervals. In addition, Bai et al compared (a) mothers with an affected sister, to (b) fathers with an affected brother, finding ASD risk in the offspring to be 1.73 (95% CIs 1.19-2.35) for the mother-sister risk and 1.63 (95% CIs 1.16-2.16) for the father-brother risk. Again, a small difference with overlapping confidence intervals. Overall, these findings lend no weight to the hypothesis that female resilience (in the context of familial/genetic risk factors) is a major factor underpinning the sex ratio in ASD.

The ability to examine the distribution of ASD within families across multiple generations is a remarkable resource and provides a demonstration of the power of health registers. The report by Bai et al/ complements other ASD-related findings based on Swedish registers, including studies describing: (a) the heritability of ASD based on monozygotic or dizygotic twins, full siblings, and paternal and maternal half siblings (2); (b) the association of advanced paternal and grand-paternal age and risk of autism (3); and (c) the association between neonatal vitamin D deficiency and an increased risk of ASD (4).

The ‘optics’ of health registers can also be improved by cross-linking with genetic data. Danish researchers have used health registers to define (a) population-based samples of people with schizophrenia (N=3540), autism (N=16,146), attention-deficit/hyperactivity disorder (N=18,726) and affective disorder (N=26,380), of which 1928 had bipolar affective disorder; and (b) a randomly selected cohort from the community (N = 30,000) (5). The iPSYCH case-cohort study is a state-of-the-art sample that is providing never-before-seen level of detail. With respect to ASD, this sample contributed the majority of the cases and controls for a recent genome-wide association study (GWAS) (6). In addition, Danish researchers have been able to link polygenic risk scores (based on genotypes derived from neonatal dried blood spots) with register-based information to explore population-based risks of developing mental disorder such as depression (7). Polygenic risk scores can also be combined with nongenetic risk factors of interest in order to explore gene-environment interplay (8). In summary, the ability to combine continuously distributed genetic risk scores with register-based variables, in a large population-based sample, is a remarkably powerful tool for modern psychiatric research (9).
Surprisingly, studies that blend health registers and genotyping can also provide valuable insight into the links between social factors and risk of mental disorders. Swedish researchers have linked (a) health registers across family units, (b) genetic information from a Swedish twin sample, and (c) small area (i.e. neighbourhood) measures of social deprivation. There is evidence to suggest that living in poorer, more deprived neighbourhoods might contribute to the risk of subsequently developing schizophrenia (via stress-related mechanisms, for example). Sariaslan et al (10) found that the association between an increased risk of schizophrenia and residence in a neighbourhood with greater social deprivation scores could be confounded by genetic selection. Their data supported the hypothesis that those with common variants linked to an increased risk of schizophrenia may be more likely to move into neighbourhood with worse social deprivation scores.

Register-based research has provided a solid foundation for psychiatric epidemiology. This commentary has sketched out examples to demonstrate how the ‘optics’ of psychiatric epidemiology are constantly being improved. Things that were previously unmeasurable can now be measured. However, we know that there is much more work to be done. Inspired by Galileo’s exploration of the solar system, we need to invent ways to detect more of the ‘dark matter’ of psychiatric epidemiology.

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