immediate results. However, complex problems are not often successfully addressed with simple solutions.

The epidemiological evidence generated in Walter and colleagues' study[2] highlights the intense susceptibility of people hospitalised for psychiatric disorders to very serious outcomes for a long time after their first hospitalisation. Many of these outcomes are not rare, and are occurring in very young people, and especially in young men, who could otherwise have many years to contribute to society. Therefore, although a more upstream approach to prevention might be disruptive and expensive in the short term, this study and other research on the developmental origins of health and disease and on the social determinants of health suggest that this approach could have the greatest long-term gain. Research to more precisely explain the mechanisms for the observed outcome disparities in this at-risk group will guide the nature of the comprehensive social and health programmes aiming to prevent them.

Simone N Vigod, Paul A Kurdyak
Women's College Hospital and Research Institute, Toronto, ON M5S 1B2, Canada (SNV); Department of Psychiatry, Faculty of Medicine and Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada (SNV, PAK); ICES, Toronto, ON, Canada (SNV, PAK); and Centre for Addiction and Mental Health, Toronto, ON, Canada (PAK)
simone.vigod@wchospital.ca

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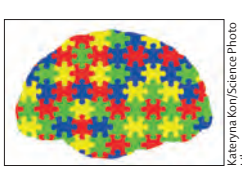
Recognising the heterogeneity of autism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Authored by 16 scientists from nine different countries, Jong Yeob Kim and colleagues' Article[1] provides a thoughtful, comprehensive review of environmental risk factors and biomarkers for autism spectrum disorder. It extends an already solid base of meta-analyses,[2,3] generally about more specific topics, by pulling information together from this base and using new statistical approaches to create an umbrella review. Compared with many of the individual reviews,[4,5] Kim and colleagues' conclusions on major environmental factors are sometimes more affirmative about their possible effects on autism spectrum disorder. This might be because this umbrella review is more comprehensive and pulls in a greater number of studies than have previous papers. However, given the less nuanced consideration of publication bias in this umbrella review than in other similar papers,[2] as well as the greater publication biases often found in papers published in high-impact journals compared with other journals,[6] the discrepancy between Kim and colleagues' results and the meta-analyses they are based on seems important. Researchers in epidemiology and all forms of science have been aware for a long time that positive findings are more likely to be published than negative results. Yet, despite systematic attempts—which are considered in this umbrella review—to address biases within individual papers, the overall bias of meta-analysing what has already been published (and not data that have gone unpublished) remains.[7] There continues to be a risk—eg, with maternal use of antidepressants during pregnancy—of overstating the size of general concerns without recognising the possible consequences of such blanket statements of risk that might actually be influenced by other factors.[4,5]

Easier to address are issues related to publication of research about autism spectrum disorders. Although autism is highly heritable, genetic causes and risks for autism are greatly variable and differentially affect individuals with autism and intellectual disability and autism without intellectual disability.[8] There also are

clear sex differences in the risk for autism, which have resulted in theories of protective factors and other differences in genetic liability. Yet, it is striking how few epidemiological studies provide information about the sex of the affected individuals and, with a few exceptions,[5] their status in terms of autism spectrum disorder with or without intellectual disability. Many years ago, studies of diagnosis and treatments of autism spectrum disorder also failed to consider this basic information, leading to confusion about what was autism and what was, in fact, severe intellectual disability. It also seems very likely that the timing of exposure to environmental factors during gestation or a child's development has at least some effect.[9]

Beyond this, consideration of reference groups for comparisons is also important. Are effects specific to autism (with or without intellectual disability) or are they relevant to other neurodevelopmental disorders? Several recent papers have sought to compare autism spectrum disorder to attention-deficit hyperactivity disorder or intellectual disability,[9] but in most cases, comparisons are to general norms. If we are going to use epidemiological findings to better understand mechanisms of risk and causality for autism spectrum disorder, we need to know more than that autism spectrum disorder is different to the overall population. Increasingly large samples yielding data that are almost impossible to interpret have little power to implicate potential biomarkers and risk factors without appropriate reference groups and patient information.

The practicalities of these recommendations are challenging but it is time to move forwards and recognise the heterogeneity of autism. It is time to directly consider that environmental effects might interact with genetic and other factors to affect autistic symptoms.[10] A start would be to carry out more targeted and prospective epidemiological studies within high-risk groups such as baby siblings and premature infants; work from datasets where genetic findings are already available such as the Simons Simplex Collection, SPARK, or AGRE;[11] expect more precision in terms of defining appropriate reference groups; and consider how environmental events are linked to the age and presumed developmental vulnerability of the child with autism and to characteristics such as sex and intellectual disabilities. Many other papers have called for these changes[3,9,12] but they are not yet evident, particularly in meta-analyses. Kim and colleagues' study thus lays the groundwork on which it is hoped new, more useful approaches, can be built.

Catherine Lord
UCLA David Geffen School of Medicine, Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA 90024, USA
clord@mednet.ucla.edu

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Which antidepressant doses are optimal?

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In the most exhaustive investigation to date—an important contribution because of its broad scope and methodological rigour—Toshi A Furukawa and colleagues[1] report findings that resonate well with earlier efforts: selective serotonin reuptake inhibitors (SSRIs) display dose-dependent beneficial effects up to the low-to-medium end of their licensed doses,[2–4] and so do mirtazapine and venlafaxine. Offsetting this