Heterogeneity in prevalence of co-occurring psychiatric conditions in autism

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In *The Lancet Psychiatry*, Lai and colleagues[1] describe the results of a systematic review and meta-analysis of the prevalence of co-occurring mental health/psychiatric conditions (CMHCs) in autism spectrum disorder (hereafter "autism"). Autism encompasses a group of neurodevelopmental conditions affecting social communication and repetitive behaviour patterns with wide variability in symptom severity, intellectual and language functioning, and co-occurring problems. There is great variability both between individuals at any specific age and within individuals across development. Addressing this clinical heterogeneity is an important challenge in any study aiming to answer a question about characteristics of people with autism "in general".

In this meta-analysis, only pooled prevalence estimates and their confidence intervals are highlighted in the abstract and main text. Confidence intervals demonstrate the uncertainty around the *average* prevalence estimate for the *average* study. However, prediction intervals are necessary to take into account between-study variability, and therefore provide important information for interpretation of results.[2,3] We would like to bring attention to the wide prediction intervals. For example, the pooled prevalence estimate for anxiety disorder diagnosis was 20% (95% CI=17-23), but based on the prediction interval, a new sample of individuals with autism can be expected to show estimates of anxiety disorder ranging between 2% and 48% (prediction interval for ADHD 4-63%, depression 0-33%, bipolar spectrum disorders 0-19%, schizophrenia spectrum disorders 0-14%, obsessive-compulsive disorder 1-21%, disruptive disorders 0-36%, and sleep-wake disorders 0-43%).

The wide prediction intervals and extreme between-study variability (I^2 exceeding 95%) make it difficult to interpret the overall prevalence estimates of CMHCs across all individuals with autism. Nevertheless, the article is important in highlighting the need for future work parsing the heterogeneity in CMHCs in autism. Focusing on well-characterized subgroups can help answer clinically relevant questions, such as what is the prevalence of anxiety disorders in school-aged males with autism and average-range intellectual functioning, or in adolescent

females with autism and intellectual disability? Lai and colleagues performed meta-regression with pre-specified potential moderators of prevalence of CMHCs, which were considered exploratory due to limited power. The ability to fully explore rates of CMHCs across specific subgroups may also be limited by poor reporting on patient characteristics. In studies regarding the prevalence of ADHD in autism, for example, nearly a third did not report on intellectual functioning. As Lai and colleagues suggest, it will be critical for future work in this area to provide more interpretable insights into CMHCs in autism across subgroups and within individuals across development.

The primary justification for meta-analysis is explained as "Accurate 'prior knowledge' of the prevalence of CMHCs in autism provides critical background information for adequate mental health evaluation and service delivery."[1] However, the meta-analysis focused on the prevalence of *clinician-assigned diagnoses* of CMHCs without any criteria for assessment of CMHCs beyond the use of ICD/DSM criteria. As acknowledged by Lai and colleagues, the way CMHCs have been diagnosed in autism by different clinicians across different countries and health care systems during the past two decades is likely to vary widely, and undoubtedly contributes to the extreme between-study variability in prevalence estimates. CHMCs might not be systematically assessed in individuals with autism, maybe especially in those with lower intellectual and language functioning. For example, a diagnosis of depression may not even be considered in someone who cannot verbally express his/her sadness.[4] Similarly, assessment measures of ADHD largely rely on assumptions of within-average range intelligence when evaluating regulation of attention, impulsivity and activity.[5] Therefore, beyond the need to consider whether apparently inattentive or impulsive behaviours are manifestations of autism symptoms, clinicians must further determine whether activity and attention is affected beyond what would be expected for developmental level.[5] The Diagnostic Manual-Intellectual Disability-2[6] was developed to assist with the challenges inherent in interpreting standard diagnostic criteria in individuals with intellectual disability (including those with limited verbal ability). Still,

use of this tool, or instruments designed for assessment of CHMCs in autism, are not necessarily standard practice.

The DSM-5 requires clinicians to consider and provide diagnostic specifiers of CHMCs and other traits with implications for prognosis and/or treatment in individuals with autism (e.g., intellectual functioning, language level and medical conditions). We hope that this will inspire more systematic assessment of CHMDs in autism. We agree fully with the authors' conclusion that the available evidence implies that "mental health assessment should be an integral aspect of clinical care with regular screening, evaluation and treatment undertaken as part of ongoing support for individuals with autism."[1]

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