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Prenatal ADHD medication and child neurodevelopment

Making sense of multiple findings from a single study

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Diagnoses of neurodevelopmental disorders such as autism spectrum disorder and attention deficit/hyperactivity disorder (ADHD) have increased in recent decades,[1,2] prompting interest in identifying modifiable risk factors. Because these disorders are typically diagnosed years after birth, research historically required costly and logistically demanding prospective cohorts.[3] Increasing access to population based health registers and administrative claims databases with longitudinal follow-up has made studying these outcomes in large populations feasible.

In a linked study (doi:10.1136/bmj-2026-101236),[4] Bruno and colleagues use linked national register data from Denmark, Norway, and Sweden to examine the association between prenatal exposure to drug treatments for ADHD and neurodevelopmental disorders in children. The study extends previous evidence by assessing three therapies separately (methylphenidate, amphetamines, and atomoxetine) and by examining a broad range of outcomes, from composite categories of neurodevelopmental disorders to specific diagnoses and other developmental conditions. A few elevated estimates were observed for infrequent outcomes, but they were not consistently replicated across analyses. The authors concluded that the findings are reassuring, an interpretation that seems to be well supported by the data and the consistency of the results with previous studies.[5-8]

The study provides a valuable opportunity to reflect on a central challenge when using large secondary data sources to evaluate drug safety in pregnancy. Randomised trials typically specify a primary outcome and determine a sample size with that outcome in mind, giving investigators a clear starting point for interpreting results. By contrast, large observational data sources make examining multiple drugs, exposure windows, and outcomes possible, as well as testing the robustness of findings across a range of sensitivity analyses. This level of granularity is crucial for answering causal questions about drug treatment in pregnancy, but the many comparisons make drawing an overall conclusion harder, especially when some estimates are based on few events. The challenge is to make sense of the wider pattern of findings rather than focusing on any single estimate.

Across the 306 weighted estimates presented by Bruno and colleagues, 15 were statistically significant at the nominal 5% level. This is about the number expected by chance alone under the global null hypothesis. This does not mean that every significant finding is spurious or that a causal effect can be ruled out for every non-significant one. Classifying estimates as "significant" or "not significant" by using a conventional P value threshold obscures the distinction between an estimate's magnitude and its precision, and it covers only random error, not systematic error.[9] Even in a large source population some exposure groups and outcomes will be uncommon, leaving estimates imprecise. For example, among 3.6 million pregnancies, Bruno and colleagues identified only 95 pregnancies with exposure to atomoxetine in the second or third trimester. With so few exposed pregnancies, even a meaningful increase in risk may not reach statistical significance, whereas a chance elevation can easily appear.

If statistical significance should not drive interpretation,[10] what should? Several considerations can help to guide the evaluation of findings.

First, magnitude. Adopting a threshold for adjusted relative risks (for example, ≥1.3 or ≥1.5) can help to identify estimates that warrant particular attention, because stronger associations are harder to explain by systematic error alone. Any such threshold is inherently subjective, and other people may reasonably prefer a different one depending on the context. When all estimates are reported, readers can apply their own. Of course, the upper limit of the confidence interval should also be considered, as it shows the largest increase in risk that remains reasonably compatible with the data, and this increase can be substantial even when the point estimate is close to the null.

Second, robustness. Confidence in a finding increases when it holds across analyses that rely on different assumptions and are vulnerable to different biases, because explaining the agreement by any one source of bias is then more difficult. The study by Bruno and colleagues is particularly strong in this regard: its secondary and sensitivity analyses cover confounding by indication, exposure misclassification, and familial confounding, and the main findings were largely consistent across them.

Third, replication. Elevated estimates that recur in independent data sources are less likely to be chance findings, although they may still reflect shared biases. When the number of events allows, presenting results stratified by cohort or country—in addition to pooled results—helps to show whether an elevated estimate is consistent across settings or driven by one of them.

Drug safety studies in pregnancy have become considerably more sophisticated,[11,12] as the linked study illustrates. The interpretation and communication of findings, however, have received far less attention, and approaches vary across studies. The considerations discussed here serve only as

examples; the field would benefit from agreement on which ones should routinely guide the interpretation of findings. Such consensus need not prescribe a single threshold or rule, but it would help clinicians to make sense of evidence across studies and support clearer conversations with patients about treatment decisions.

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