The study by Sundbakk et al\textsuperscript{1} found no increased risk of attention-deficit/hyperactivity disorder (ADHD) in offspring who were exposed to benzodiazepines or z-hypnotics in utero after analyzing data from the Norwegian Mother, Father and Child Cohort Study (MoBA). Among the 82,201 pregnant individuals with live births included in the study, 0.8\% self-reported any use of benzodiazepines or z-hypnotics in at least one 4-week interval throughout the pregnancy. Offspring were followed up for a mean period of 11.3 years through a linkage to the Norwegian national registries for diagnosis of hyperkinetic disorders or a prescription for an ADHD medication. The authors' primary analysis considered the timing of exposure (early or middle and/or late pregnancy) compared with pregnant individuals without benzodiazepine or z-hypnotic exposure during pregnancy among all pregnancies and among pregnancies with documented indications (depression, anxiety, sleeping problems, or other mental health conditions). Additionally, the authors examined the association between the number of exposed intervals during pregnancy and ADHD. Results suggested no association of benzodiazepine or Z-hypnotic use with childhood ADHD; however, an increased risk with use in 2 or more 4-week intervals compared with only 1 exposed interval could not be ruled out.

Globally, the prevalence of benzodiazepines and z-hypnotics (also known as benzodiazepine-related drugs) in pregnancy is estimated at 1.9\%.\textsuperscript{2} Benzodiazepines are primarily indicated for anxiety and insomnia but are commonly prescribed for other psychiatric and nonpsychiatric indications, including depression and chronic pain. Although benzodiazepines and z-hypnotics are typically recommended as a short-term treatment of less than 4 weeks, longer-term use is frequent. These medications can be taken as needed or intermittently, adding to the challenges and difficulties of studying the risks or benefits of these drugs in pregnancy.

The work by Sundbakk et al\textsuperscript{1} adds to previous MoBA cohort studies on the association between benzodiazepine and z-hypnotic use in pregnancy and ADHD symptoms. Using a similar design, Lupattelli et al\textsuperscript{3} reported no clinically meaningful association between these medications in middle or late pregnancy and ADHD symptoms at age 5 years, as measured with the Conners Parent Rating Scale-Revised, with the exception of a small increase in ADHD symptoms after benzodiazepine monotherapy in late pregnancy. The primary difference between the study by Sundbakk et al\textsuperscript{1} and the study by Lupattelli et al\textsuperscript{3} was the outcome definition. Sundbakk et al\textsuperscript{1} defined ADHD by diagnoses and prescription fills found in inpatient, specialist, and dispensing records, whereas Lupattelli et al\textsuperscript{3} measured ADHD symptom scores reported in a validated questionnaire. Each outcome definition had strengths and weaknesses. Clinical diagnosis or treatment records capture cases that are severe enough to require medical attention but could be subject to detection biases (eg, likelihood of seeking care may differ by parental health status). In contrast, symptom scores may capture a broader range of symptoms and patients but are potentially biased depending on the scales' reliability and validity.\textsuperscript{4} Consistent results across these outcome measurements strengthen the conclusion that benzodiazepines and z-hypnotics are not likely to be important factors in childhood ADHD.

Still, the body of literature on this topic remains limited. Both the Sundbakk et al\textsuperscript{1} and Lupattelli et al\textsuperscript{3} analyses are the only 2 studies, to our knowledge, to have directly assessed ADHD or ADHD symptoms. Studies that measured related behavioral problems after benzodiazepine or z-hypnotic
exposure in utero found either no association or a moderate association.\textsuperscript{5,6} Two recent systematic reviews on the neurodevelopmental safety of benzodiazepines and z-hypnotics concluded that, although these medications are unlikely to be major risk factors for behavioral and other neurodevelopmental disorders, the heterogeneity of study design and overall scarcity of data preclude definitive conclusions.\textsuperscript{5,6}

The findings by Sundbakk et al\textsuperscript{1} are reassuring overall, but some findings require additional investigation. Comparing use in multiple 4-week periods with use in a single 4-week period showed that the hazard ratio for ADHD was consistent with a 32\% to 48\% increase in ADHD, although the 95\% CIs were wide. Similarly, in the Lupattelli et al\textsuperscript{3} analysis, use in multiple 4-week periods was associated with a small increase in ADHD symptoms. These results may suggest an association between increased risk and continued benzodiazepine or z-hypnotic use in pregnancy. A limitation of the exposure assessment was that the drug frequency or dose within each 4-week interval of pregnancy was not measured. Use in a single 4-week period may represent 28 days of use or 1 day of use. Therefore, pregnant individuals who indicate use during multiple 4-week periods may not actually have more exposure during pregnancy than individuals who indicate use in a single 4-week period. The mixing of long-term and intermittent users among individuals with exposure in multiple 4-week intervals may also lead to residual confounding by indication. Evaluating the safety of these medications across different patterns of use during pregnancy, especially long-term use, is of particular importance in future research.

Accurately classifying medication exposures in pregnancy is challenging given that individuals may discontinue or modify medication use after learning they are pregnant. Benzodiazepines and z-hypnotics may be used as needed, adding to this complexity. Self-report may be a more accurate indicator of actual benzodiazepine and z-hypnotic consumption and timing during pregnancy than dispensing and prescription records. Sundbakk et al\textsuperscript{1} cited a MoBA study that compared self-reported benzodiazepine use with dispensed prescriptions during pregnancy and found that self-reported use had a sensitivity of 45\% and specificity of 99.7\%.\textsuperscript{7} This finding meant that 45\% of pregnant individuals with a dispensed benzodiazepine prescription in pregnancy self-reported use during pregnancy, and 99.7\% of pregnant individuals without a dispensed benzodiazepine prescription in pregnancy self-reported no benzodiazepine use during pregnancy. Self-reported use can also be misclassified; for example, intermittent users may forget the specific timing of use, or pregnant individuals may not want to report their use of some medications. However, these data suggest that use of dispensing records alone to define benzodiazepine exposure could lead to misclassification of a large number of nonusers as users and put results at risk of substantial bias from exposure misclassification.

Overall, we believe these results are reassuring for individuals who require treatment with benzodiazepines and z-hypnotics during pregnancy. Most of the research on benzodiazepine and z-hypnotic safety in pregnancy for ADHD and behavioral outcomes has been conducted within the MoBA population; therefore, results need to be replicated in other populations before definitive conclusions can be made. Large sample sizes will be necessary for considering the duration of use and dose and for examining benzodiazepines and z-hypnotics separately. Questions surrounding long-term use remain, and additional neurodevelopmental outcomes need to be studied. Caution must be exercised when using these medications during pregnancy and when identifying situations in which therapeutic alternatives may be more appropriate, especially when use is long term.\textsuperscript{8}
REFERENCES


