## Re: Neonatal Abstinence Syndrome and High School Performance

The authors are commended for attempting to elucidate the poorly understood consequences of neonatal abstinence syndrome (NAS), a current global public health concern.[1] Contrasting school test results from children diagnosed with NAS with matched controls and other children, the authors conclude that NAS is "strongly associated with poor and deteriorating school performance." Determining academic risk for substance-exposed children could inform the need for early intervention services; therefore, the information could be important. We are concerned that this conclusion is not supported by the methodological approach, potentially leading to inaccurate perceptions by the public and policymakers.

The article uses only minimal criteria to match NAS cases. Mothers of infants of matched controls were older, far less likely to be Indigenous, with more education and more antenatal care; control infants had higher birth weights and were less likely to be admitted to an ICU. The baseline differences between groups increase the likelihood that observed associations were the result of unmeasured confounding. Unevaluated were myriad critical factors that significantly affect the developing child, including antenatal and postnatal maternal substance use and treatment, NICU versus other NAS care, length of NAS pharmacotherapy (if all cases received pharmacotherapy), child custody, violence exposure, psychiatric comorbidity and medications, poverty, lack of medical care, or any number of other factors that could independently or collectively affect development of a child of a mother with a substance use disorder.

Second, the diagnosis of NAS is potentially oversimplistic and represents a heterogeneous group of diagnoses ranging from any (minor) symptom of opioid withdrawal, opioid withdrawal necessitating treatment, or withdrawal symptoms caused or potentiated by other substances (such as selective serotonin reuptake inhibitors, alcohol, nicotine, benzodiazepines). Maternal polysubstance use is common among high-risk populations, and other antenatal exposures, such as teratogenic alcohol, could have an independent effect on school test performance. Because the population of mothers of infants with NAS is more likely to be Indigenous, and this status is related to higher alcohol consumption,[2] this missing variable is notable. Similarly, nicotine exposure, also more likely in Indigenous pregnant women,[3] is another important and unrecognized consideration. Lastly, there are multiple determinants of school performance, and reliance on standardized testing alone, particularly for Indigenous children, is overly simplistic in that it neglects the school environment and other factors affecting student engagement.[4]

Consequently, study results should be interpreted cautiously. Our principal concern is that the conclusion that NAS is associated with poor school performance will hark back to the "crack baby" epidemic of the 1980s; it took years of research to undo the damage that early reports of lower IQ in cocaine-exposed children portended. Many women with opioid use disorders seek necessary medication-assisted treatment, which can imply risk for NAS in the infant. The perhaps inaccurate association between NAS and poor academic outcomes may drive women away from essential treatment, which is damaging to public health. Long-term outcomes of opioid-exposed infants and those with NAS remain an important area of inquiry. There is an urgent need for well-funded, prospective studies evaluating developmental outcomes of this vulnerable population.

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## Authors' Response

We thank Prof Terplan and colleagues for their commentary on our article. We agree that the criteria used to define NAS in our study were restrictive (International Classification of Diseases, 10th Revision code P96.1) and that there was no information on important clinical and social details that may have had potential impact on a child's learning ability, such as type of specific drug exposure or social issues.

This is indeed a deficiency that is well acknowledged by studies based on administrative data but is not a reason

to ignore such data, which should be used cautiously to inform future policy and practice. Acquiring alternative data from individual patients on a large scale will be prohibitively expensive and may not be feasible because of the cost and possibly high attrition rates in such a chaotic population.

We agree that our results must be interpreted cautiously but do not believe that our study represents "an inaccurate association . . . [that] may drive women away from essential treatment." Mothers cannot be stopped from using drugs. Many mothers need drugs for their physical and psychological health, and some of these drugs may also cause NAS. Our study does not provide proof of causality, despite the demographic control variables used. What we present, rather, are novel data associating a diagnosis of NAS with poor school outcomes, which, regardless of the cause, allows early identification and intervention for the children, which in high-risk populations can lead to benefits for the children and their families, even in the second or third decade of life.

Current resources, both research and clinical, are overwhelmingly focused on hospital treatment of NAS. There is little information or guidance for clinicians or policymakers for the management of children and families affected by NAS beyond infancy. Academic success contributes to well-being and radically improves the chances for a child becoming a productive adult rather than a drain on society. With the right type of support, any child can perform better at school, and this effect has been shown to flow on for decades and even until subsequent generations. Ignoring this effect in a population that is easily identifiable from birth will do a great disservice to thousands of children and families worldwide.

We therefore strongly agree with Prof Terplan and colleagues' suggestion that "well-funded, prospective studies" must be urgently conducted so that we can learn how to prevent more harm to an already vulnerable population, but rather than stopping at hospital discharge, support and care for children with NAS must be continued beyond infancy and beyond resolution of NAS.

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