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COMMENTARY

The Apgar paradox

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Most of today's readers of this journal will have received an Apgar score 1 and 5 min after birth. The measure was introduced by Virginia Apgar, an anesthesiologist, in 1952; and, since the 1960s, it is popular world-wide. The Apgar score is now ubiquitously used in newborns and arguably the most common composite screening instrument in medicine and only a few single measure screening procedures such as growth curves, glucose levels or blood pressure are more frequently employed.

In the Apgar score, neonates are assigned a numerical score of 0–2 for heart rate, respiratory rate, skin color, muscle tone, and response to stimuli resulting in a score of 0–10. The score is measured at specific periods after birth, generally 1, 5 and 10 min. The score at 1 min reflects successful transition from the womb; that at 5 min the successful adaptation to extra-uterine life, with or without medical intervention. Generally, a score of <7 at 5 min is considered to present a risk of poor birth outcome, and scores in the 1–4 range are ominous.

In the current issue of the European Journal of Epidemiology, Modabbernia and colleagues associate Apgar scores to the risk of autistic disorder (AD) and autism spectrum disorder (ASD) [1]. The results confirm a meta-analysis of six population-based studies [2], and the sample size is impressive, more than 5.5 million individuals with an Apgar score were included. The cases were ascertained in routine care in Norway, Sweden, Denmark and Australia and data were provided by registries that have typically demonstrated high diagnostic validity. Continuous analysis showed a dose response relation in the range of 4–10, where lower Apgar scores were linearly associated with a higher risk of ASD and AD. However, below an Apgar score of 4, the risk did not increase any further. The authors demonstrate that these associations were not explained by low birth weight or gestational age at birth. They carefully discuss the role of missing confounders such as socio-economic status and parental psychopathology. Also, in line with current scientific practice, the authors avoid causal inference carefully with one exception in the context of stratified analyses: "[the] effect of low Apgar score on risk of ASD". Finally, the authors acknowledge that the absolute risk of ASD/AD in children with a low Apgar score is small. This statistical association study is state of the art.

The combination of four large population based national cohorts enables the authors to perform stratified analyses such as those by sex. In girls a low Apgar score contributed slightly more to the risk of ASD than in boys. Although the magnitude of the sex interaction was small, this raises the question whether AD as currently diagnosed in girls may have a different etiology than AD in boys. Another in-depth analysis made possible by the large sample size focusses on the 8430 children with a very low Apgar score of 1–3. The children with an Apgar score of 1–3 had no higher risk of ASD than children with a score of 4–7. The absence of a dose–response relation at the end of the distribution is attributed to diagnostic overshadowing, i.e., children are diagnosed with intellectual disability or cerebral palsy. A substantial diagnostic bias with under-diagnosis is one plausible explanation, although some may argue that ASD (which included pervasive developmental problems before 2000) was over-diagnosed in persons with intellectual disability or sensory impairment [3]. Alternatively, some factors contributing to a very low Apgar score may not be causal. This is not discussed by the authors although a seminal meta-analysis of Gardner et al. [4] concluded "the factors with the strongest evidence against a role in autism risk included previous fetal loss and maternal pre-eclampsia, proteinuria, hypertension and swelling". In contrast, they identified prenatal risk factors for autism such as maternal age, gestational diabetes, or higher parity, which are recognized as background risk factors in obstetric care. The work of Modabbernia and colleagues raises an important question for future research: does the lack of a dose–response effect point us to the absence of causal mechanisms? Can we use

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registries to conduct studies of both sets of obstetrical conditions in relation to ASD or AD?

Some potential difficulties of the study are not considered; the first is misclassification of the outcome. While they argue that the cases in the registry are highly valid, they present no estimates of children with autism who may not be included in the registries, e.g., by virtue of age (diagnoses up to early school age will capture more severe autism than later ages), or diagnostic practices. For example, prior to 1994, only inpatient diagnoses of autism were included in the Danish registry with both inpatient and outpatient diagnoses recorded later [5]. Only if the missed cases had similar Apgar score as those in the registry, the estimates of association would be accurate.

Second, and perhaps more important, is the difficulty in interpreting what the Apgar score is measuring. Although a convenient short-hand method for characterizing the status of the newborn, both obstetric and pediatric professional associations continue to emphasize the limitations of the score. It suffers from low reliability depending on the professional making the assessment and the context of the delivery. For example, healthy preterms are likely to be misclassified, and factors such as maternal drug use, infections, and hypovolemia may affect infant responses [6]. While lower Apgar scores are considered a risk, they provide no clear indication as regarding resuscitative actions or diagnostic information. It is not even clear what they are a "risk" for, as the score lacks sensitivity and specificity for most perinatal outcomes, even that of low scores for cerebral palsy.

The etiology of autism is largely genetically determined, although environmental factors clearly play a role. In their pursuit of autism etiology, many researchers attempt to assess very early symptoms and endophenotypes of autism in population-based studies or high risk cohorts. Examples of such markers of autism include poor social visual engagement at 20 months [7] and atypical head movement signatures at 2 months [8]. Our group showed that low muscle tone in a neurological examination at 6 weeks precedes autistic traits [9]. The children in the study of Modabbernia et al. are younger still, 5 min old exactly. Interestingly, low muscle tone, which predicts autistic traits, is a vital body sign included in the Apgar. Perhaps precursors or prodromal symptoms of autism are what affects the Apgar score. Without the ability to examine the individual components of the Apgar score, this issue cannot be resolved. The causes and consequences of low tone, an important early neurological sign, should be studied further.

If the results are not very novel, a low Apgar score has no relevant predictive value, causality cannot be inferred, and the statistical association can easily be attributed to a myriad of very different and complex underlying factors, why bother? This is the paradox of the Apgar score; most, if not all pediatricians and obstetricians know of its major limitations. Yet, more than 65 years after its development hardly any better predictor of childhood morbidity has been developed and widely implemented. Newborn severity scores are used successfully to understand factors leading to mortality and variations in outcome by different institution, but these scores have not been incorporated in registries or birth certificates and pertain to only certain births, e.g., very preterm births [10]. Hence, to this day well-conducted research continues to utilize the Apgar scoring system to try and build up incremental knowledge. Our understanding of the biological mechanisms underlying the relation of obstetric complications with neurodevelopmental disorders remains limited as few studies provide clues how to proceed in this scientific endeavor. That, however, is what Modabbernia and colleagues' study achieved.

References

1. Modabbernia A, Sandin S, Gross R, Leonard H, Gissler M, Parner ET, Francis R, Carter K, Bresnahan M, Schendel D, Hornig M. Apgar score and risk of autism. Eur J Epidemiol. 2019. https://doi.org/10.1007/s10654-018-0445-1.
2. Modabbernia A, Mollon J, Boffetta P, Reichenberg A. Impaired gas exchange at birth and risk of intellectual disability and autism: A meta-analysis. J Autism Dev Disord. 2016;46(5):1847–59.
3. Hoevenaars-van den Boom MA, Antonissen AC, Knoors H, Vervloed MP. Differentiating characteristics of deafblindness and autism in people with congenital deafblindness and profound intellectual disability. J Intellect Disabil Res. 2009;53(6):548–58.
4. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry. 2009;195(1):7–14.
5. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA. 2003;290(13):1763–6.
6. American Academy of Pediatrics. American college of obstetricians and gynecologists, committee on obstetric practice. The Apgar score. Pediatrics. 2006;117(4):1444–7.
7. Constantino JN, Kennon-McGill S, Weichselbaum C, Marrus N, Haider A, Glowinski AL, Gillespie S, Klaiman C, Klin A, Jones W. Infant viewing of social scenes is under genetic control and is atypical in autism. Nature. 2017;547(7663):340.
8. Denisova K, Zhao G. Inflexible neurobiological signatures precede atypical development in infants at high risk for autism. Sci Rep. 2017;7(1):11285.
9. Serdarevic F, Ghassabian A, van Batenburg-Eddes T, White T, Blanken LM, Jaddoe VW, Verhulst FC, Tiemeier H. Infant muscle tone and childhood autistic traits: a longitudinal study in the general population. Autism Res. 2017;10(5):757–68.
10. Richardson Douglas K, et al. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. J Pediatr. 2001;138(1):92–100.