This Month In The JOURNAL of PEDIATRICS

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Childhood risk factors and adult cardiovascular disease

— Stephen R. Daniels, MD, PhD

The issue of whether risk factors in childhood and adolescence increase the risk of cardiovascular disease in adulthood is a very important question with major potential clinical implications. However, creating recommendations in this area has been difficult because of a lack of direct evidence linking early risk factors, such as obesity, diabetes, hypertension, dyslipidemia, and cigarette smoking with the occurrence of myocardial infarction and stroke 30-60 years later. It is easy to understand why such evidence is sparse because studies showing such relationships would have to follow individuals for a very long period of time. However, evidence along these lines is beginning to emerge.

In this volume of *The Journal*, Pool et al present a systematic review of this emerging evidence. They found consistent associations between childhood risk factors, such as adiposity and hypertension, and adult cardiovascular disease. They found little evidence for other childhood exposures, such as diet, physical activity, and early life exposures. It is important to know that there is good evidence for some of these relationships as this may inform clinical recommendations. It is also important to know which variables need to be studied, as this will help inform the design of future studies. However, these new studies will need to achieve long-term follow-up to provide definitive answers.

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Umbilical cord milking should be avoided in preterm infants

— Robin H. Steinhorn, MD

Placental transfusion, or delayed cord clamping (DCC), is now standard delivery room care for term and vigorous preterm infants due to its benefits on survival and neurodevelopmental outcome. Umbilical cord milking (UCM) hastens placental transfusion via active squeezing of the umbilical cord before it is cut and has been proposed as a method that might benefit depressed preterm infants by allowing more rapid initiation of resuscitation measures.

Although early pilot trials of UCM in extremely preterm infants were encouraging, an international randomized control trial (*JAMA* 2019;322:1877-86) and a retrospective cohort study by the Canadian Neonatal Network (*J Pediatr* 2020;225:58-64) inserted caution: both studies found higher rates of severe intraventricular hemorrhage in preterm infants (<32 weeks of gestation) exposed to UCM compared with DCC. In this volume of *The Journal*, Kumbhat et al report strikingly similar associations between UCM and severe intraventricular hemorrhage (aOR 1.70 for UCM vs DCC; 95% CI 1.20, 2.43) based on their retrospective analysis of infants <29 weeks' gestation from the NICHD Neonatal Research Network.

Neonatologists know all too well that long term follow-up is essential before firm conclusions can be drawn about the effects of any intervention, and none of these 3 studies have reported neurodevelopmental data. In addition, new randomized controlled trials are underway to determine whether resuscitation with ventilatory assistance prior to umbilical cord clamping is safe and effective. While we wait for

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these results, the safest practice for preterm infants appears to be delayed cord clamping for vigorous infants, or immediate cord clamping for those that require immediate resuscitation.

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Interceding in the relationship between maternal education and academic achievement

— Denise M. Goodman, MD, MS

The root of the word "meditation" is the Latin "mediare," meaning "to be in the middle" or "to intercede" according to Dictionary.com. This is exactly what Reina-Gutierrez et al describe in a secondary analysis of a cluster randomized controlled trial (the MOVI-daFIT! Study), which sought to assess the effectiveness of a physical activity initiative to improve cardiorespiratory fitness (CRF), executive function, and academic achievement (**Figure**). There is a growing body of literature suggesting that maternal education is related to academic achievement, that CRF is related to academic achievement, and that maternal education is related to physical activity and CRF. How to disentangle these relationships? The authors took the approach of mediation analysis, finding that, for boys at least, a little over 6% of the relationship between maternal education and academic achievement is mediated by CRF.

Mediation analysis is an attempt to deconstruct some of the causal relationships when associations are observed (*J Pediatr* 2020;227:328-30) (Br J Anaesth 2020;125:398-405). Determining the direction of influence can be difficult, and advanced statistical techniques can help illuminate these issues. The difference between a confounder and a mediator is key – both are related to both the exposure and the outcome, but the mediator lies on the causal pathway while the confounder does not. Moreover, a confounder often predates an exposure, while conceptually a mediator must occur after an exposure, accounting for some indirect effect on the outcome.

Although mediation analysis relies on its own set of assumptions, similar to other approaches to data interpretation it holds promise of providing an incrementally improved and nuanced understanding of complex interactions.

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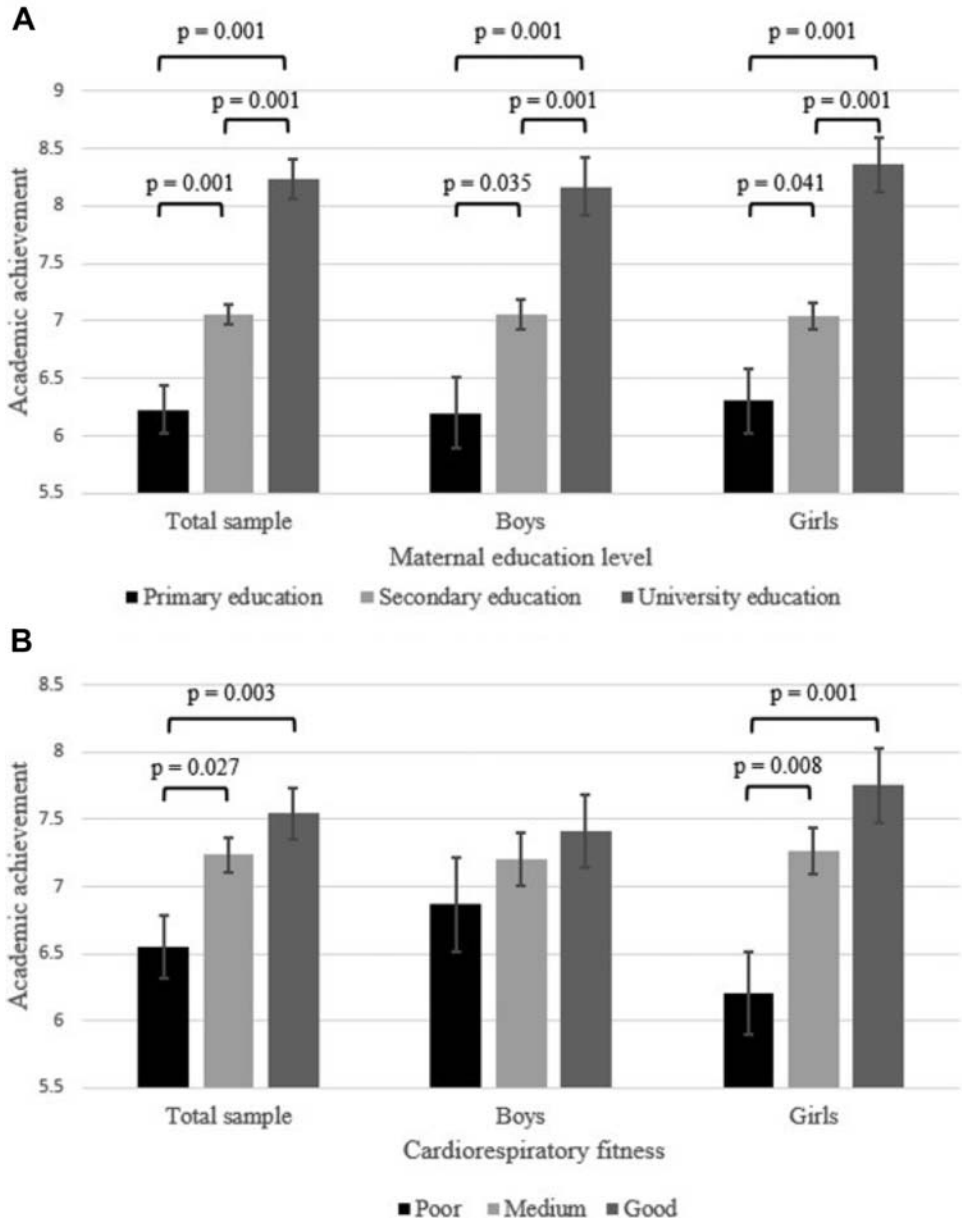

Figure. Mean differences in academic achievement by, **A**, maternal education level and **B**, cardiorespiratory fitness categories controlling for each other, by sex. Categories of cardiorespiratory fitness are poor (first quartile), medium (second and third quartiles), and good (fourth quartile). Brackets indicate significant differences in mean ($P < .05$) between categories in the Bonferroni multiple comparison post hoc test. Error bars represent standard error.