We read with interest the paper by Huang et al. (1) suggesting that neonatal jaundice is associated with childhood asthma. Using data from the Collaborative Perinatal Project (CPP), Huang et al. examined whether the associations between neonatal jaundice and childhood asthma could be due to phototherapy (which was unavailable at the time of the CPP) or a high bilirubin level itself, but the accompanying commentary (2) raised the issue of a potential common cause for both childhood asthma and hyperbilirubinemia, among other possible explanations.

We suggest that such a common cause is likely to be maternal asthma, based on our recent findings on the neonatal health of infants born to mothers with asthma (3). We found an increased risk of hyperbilirubinemia (odds ratio = 1.09, 95% confidence interval: 1.04, 1.14) associated with maternal asthma after adjustment for detailed demographic and clinical information from a large US cohort study of electronic medical records. Given that maternal asthma is known to increase the risk of asthma among offspring (4), maternal asthma is a plausible common cause that has not (to our knowledge) been considered in the literature.

These relationships are bound to be complex, and careful attention is needed to properly model the potential confounders and mediators of maternal-infant-childhood associations (5). In this case, Huang et al. adjusted their results for maternal allergic conditions (1), but this is a poor proxy for maternal asthma, since about half of current asthma is nonallergic and perhaps 30% of nonasthmatics have a common allergy response. On the other hand, we recognize that the differences between asthma diagnosis and treatment in the 1960s and in the present day add further complexity to the interpretation of these findings. This is an intriguing area of research.
and given the high prevalence of asthma in contemporary pregnancy cohorts, it merits further attention.

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REFERENCES


We thank Mendola et al. (1) for their interest in our work (2). In the invited commentary accompanying our article, Kuzniewicz et al. (3) questioned whether the association between neonatal hyperbilirubinemia and asthma was due to confounding by breastfeeding or Rh isoimmunization. Likewise, Mendola et al. are concerned about confounding by maternal asthma (1).

We created the model of the association between bilirubin level and asthma by putting each potential confounder into the model one at a time (2). However, the β coefficient of the exposure changed very slightly for breastfeeding, probably because of the small difference in the prevalence of breastfeeding between asthma (16.1%) and nonasthma (17.1%) groups in this study. Consequently, breastfeeding was not included in the final model. Similarly, only 0.70% and 0.81% of subjects in the asthma and nonasthma groups had Rh isoimmunization. When we excluded them from the analysis, the association remained unchanged. Finally, although the prevalence of childhood asthma was much higher among those whose mothers had asthma (14.3%) than among those whose mothers did not have asthma (4.5%), the prevalence of maternal asthma did not vary by bilirubin level (2.31%, 2.36%, 2.34%, 2.29%, and 2.33% in children with bilirubin levels of \( \leq 3 \), 3.1–6, 6.1–9, 9.1–15, and >15 mg/dL, respectively). As a result, the β coefficient did not change when we controlled for maternal asthma in the model.

We agree that the diagnosis of asthma has changed over time. However, the misclassification of asthma may not necessarily differ in high- and low-bilirubin groups. This nondifferential misclassification in terms of bilirubin level may have biased the results toward the null. On the other hand, considering that the prevalence of childhood asthma in this study was 5.26% in the 1960s and 1970s (2), the misclassification might not have been substantial.

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REFERENCES


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