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Title

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Permalink

https://escholarship.org/uc/item/3t06r3pw

Journal

American Journal of Epidemiology, 178(12)

ISSN

0002-9262

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Publication Date

2013-12-15

DOI

10.1093/aje/kwt249

Peer reviewed

Invited Commentary

Invited Commentary: Does Neonatal Hyperbilirubinemia Cause Asthma?

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In an analysis of data from the US Collaborative Perinatal Project, Huang et al. (*Am J Epidemiol*. 2013; 178(12):1691–1697) report an association between neonatal total serum bilirubin levels and childhood asthma. To consider the implications of this finding, we need to evaluate whether the association is causal. The results do not appear to be due to chance or any obvious biases. It is likely that the observed association is the result of a common cause of both hyperbilirubinemia and asthma (confounding). Polymorphisms in the glutathione S-transferase gene are a potential genetic confounder. The glutathione S-transferase M1-null phenotype has been linked to both neonatal hyperbilirubinemia and asthma in several studies. Before making any changes in practice aimed at lowering peak bilirubin levels to reduce asthma risk, it is vital to determine not only whether the association between higher bilirubin levels and asthma risk is causal, but also whether interventions to reduce peak bilirubin levels (or their duration) are associated with decreased risk of asthma (without evidence of other adverse effects). The study by Huang et al. should encourage further investigation of these questions.

asthma; glutathione S-transferase; hyperbilirubinemia; jaundice; neonate; phototherapy

Abbreviations: CI, confidence interval; CPP, Collaborative Perinatal Project; GST, glutathione S-transferase; OR, odds ratio; TSB, total serum bilirubin.

In an analysis of 40- to 50-year-old data from the US Collaborative Perinatal Project (CPP), Huang et al. [1] report an association between neonatal total serum bilirubin (TSB) levels and asthma diagnosis before age 7 years with an odds ratio of 1.61 (95% confidence interval (CI): 1.04, 2.08) for a maximum TSB level greater than 15 mg/dL. The association is potentially important because both neonatal jaundice and asthma are common. To consider the implications of this finding, we need to evaluate whether the association is real, causal, and generalizable, and if it is, what implications it has for clinical practice and future research.

IS THE ASSOCIATION REAL?

In an observational study, there are 4 possible explanations, other than cause-effect, for an association between a predictor and an outcome. These are chance, bias, effect-cause, and confounding [2]. With both chance and bias, the association is spurious (i.e., it exists in the study, but not in the target population).

The likelihood that the association is due to chance is based on the evidence against the null hypothesis provided by statistical analysis, as well as the prior probability of the association, based on biological plausibility and previous studies. The *P* values for the adjusted trend analysis between TSB level and asthma were small ($P = 0.009$ for TSB at 48 hours postpartum and $P = 0.008$ for maximum TSB). This suggests that the trend was unlikely to have occurred by chance, although the confidence intervals for the individual adjusted odds ratios either overlapped or barely excluded 1.0.

The prior probability of an association was at least moderate, because at least 2 previous groups have found a similar magnitude of association. In studies from Sweden, Aspberg et al. found that phototherapy and/or jaundice was associated with increased odds of hospitalization for asthma (adjusted odds ratio (OR) = 1.27, 95% CI: 1.08, 1.50) [3] and of prescription of asthma medication (adjusted OR = 1.30, 95% CI: 1.16, 1.47) [4]. Ku et al. [5] found a similar association between a diagnosis of jaundice and asthma in Taiwan, with an adjusted odds ratio of 1.64 (95% CI: 1.36, 1.98).

Other studies, however, are less consistent. A report from Kaiser Permanente Northern California found no hint of excess outpatient visits for asthma among infants who had elevated neonatal TSB levels, whether or not they were treated with phototherapy (6). However, that study was limited to outpatient visits in the first year after birth, whereas other studies included asthma diagnosed at older ages. Given the high prevalence of both asthma and neonatal jaundice, it is quite possible that additional studies or analyses showing no association exist but have not been published. The publication of the study by Huang et al. (1) should lead to additional studies on this topic, which should increase our confidence in estimates of the magnitude of the association.

There do not appear to be any biases (systematic errors) that would lead to the results of the study. Besides prematurity and low birthweight, the only other exclusion was infants with neonatal respiratory disease. The authors felt that these infants may be at greater risk for high bilirubin levels, as well as asthma. Because neonatal respiratory disease presents at or soon after birth, before the development of jaundice, an increased incidence of asthma with neonatal respiratory disease could theoretically be mediated through increased bilirubin levels. Excluding these infants only made finding an association between bilirubin levels and asthma more difficult.

TSB levels were measured in all infants at specified times, well before the diagnoses of asthma, so any bias in measurement of the predictor variable would likely be nondifferential with respect to asthma, only attenuating the observed associations. The outcome of asthma was determined by health examinations at 8 months and at 1, 3, 4, and 7 years of age. Although those diagnosing asthma may not have been deliberately blinded to perinatal bilirubin levels, it seems unlikely that they knew or cared what the bilirubin levels were, because interest in this association is a recent phenomenon. Finally, because diagnoses of asthma may have been less accurate 40–50 years ago, there may be some misclassification of outcomes. However, such nondifferential misclassification would have attenuated the association.

IS THE ASSOCIATION CAUSAL?

Another potential explanation for an association is effect-cause, rather than cause-effect. This is not a concern in this study, because high bilirubin levels occur in the first 1–2 weeks after birth, and asthma does not occur until much later.

A common cause of both hyperbilirubinemia and asthma (confounding) could also explain the observed association. The authors adjusted their analysis for known confounders, such as race and gestational age. A key strength of the analysis by Huang et al. of the venerable CPP data set is that the association of bilirubin with asthma is free from the potential confounding or mediating effects of phototherapy, which was not yet used at the time of the CPP.

Breastfeeding is known to be associated with higher bilirubin levels (7–9) and was not controlled for in the analysis. However, breastfeeding was uncommon in the CPP cohort (about 17%) and was not associated with asthma in the bivariate analysis (1). To the extent that breastfeeding is associated with decreased risk of asthma (10–12), failure to control for it would only attenuate the association between TSB levels and asthma.

The most likely confounder is a genetic predisposition to both hyperbilirubinemia and asthma. As noted by Huang et al., 1 potential example is polymorphisms in the glutathione S-transferase (GST) gene, which have been linked to both neonatal hyperbilirubinemia and asthma (13–19). GSTs can function both as enzymes and as intracellular binding proteins for nonsubstrate ligands such as bilirubin and bilirubin conjugates, decreasing reflux from the hepatocytes back into plasma (20). GST plays a role in cytoprotection and detoxification and is widely expressed in human airways.

Ghany et al. (13) and Muslu et al. (15) showed that total bilirubin levels were higher in hyperbilirubinemic neonates with the GSTM1-null genotype compared with those with the wild genotype. Multiple meta-analyses on the association between GST genes and asthma have had conflicting results and have been hampered by study heterogeneity (16–19). However, the GSTM1-null genotype may be associated with an increased risk of childhood asthma, especially in Caucasians and African Americans. Thus, the observed association in the study between bilirubin levels and asthma may be secondary to a gene polymorphism increasing an individual's susceptibility of developing both of these outcomes. This is also plausible because the polymorphism is not rare; the frequency of the GSTM1-null genotype is approximately 50% in Caucasians and approximately 20% in African Americans (21).

Lastly, although it seems to us unlikely, the association seen in the study may in fact be causal. In examining the evidence for causality, we also look at the consistency of results, the strength of the association, the consistency of a dose-response relationship, and biological plausibility. As discussed earlier, 2 other research groups found similar associations (3–5). Although the test for trend was statistically significant, the dose-response relationship was neither steep nor completely consistent, and a dose-response relationship would also be seen if the association was due to confounding.

Confounding by genetic factors such as polymorphisms in the GST gene seems more biologically plausible than a causal effect of bilirubin on asthma. The interaction between environmental pollutants and/or allergens, inflammatory mediators, and cellular response is thought to play a crucial role in the pathogenesis of asthma (22–24). Reactive oxygen species generated by both cellular metabolism and environmental pollutants result in oxidant injury and contribute to the severity and symptom exacerbation of asthma (25–27). This injury is countered by both enzymatic and nonenzymatic antioxidants, which include vitamin C, vitamin E, and glutathione (26). Glutathione plays a major role in the regulation of inflammatory responses, and GSTs catalyze the conjugation of electrophilic compounds to glutathione. It seems unlikely that bilirubin would lead directly to an increased incidence of asthma, because it is a well-known antioxidant and would protect against oxidative damage (28–30). This would favor T-helper 2 → T-helper 1 switching, thus preventing allergic disease later in life (31). Oxidative damage to the respiratory tract in the newborn may predispose an infant to asthma later in life. The role of oxidative stress on the switching of T-helper 2 → T-helper 1 subpopulations in newborns has not been fully elucidated.

IS THE ASSOCIATION GENERALIZABLE?

A major limitation of the study is that much has changed in the last 40–50 years, including dramatic increases in the incidence of asthma and the prevalence of breastfeeding (a major risk factor for hyperbilirubinemia) in the newborn period. Rhesus isoimmunization was a much more common cause of hyperbilirubinemia at the time of the CPP, but the direct antiglobulin test was positive in only 2.6% of the CPP cohort. Lastly, the population consisted mainly of Caucasians and African Americans, and no analyses to examine possible effect modification by race were presented, presumably because of limited power to examine racial differences.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

To further elucidate the relationship between bilirubin levels and asthma, additional studies and analyses are needed. It may be possible to examine the differences in asthma in previous randomized controlled trials of phototherapy (e.g., the National Institute of Health phototherapy trial from the 1970s (32)). With the availability of data on age-specific neonatal bilirubin levels, gestational age, and direct antiglobulin test results, an observational study could control for confounding by indication and examine the possible effects of hyperbilirubinemia versus phototherapy in a more recent cohort. We are currently working on such analyses (33).

If the mechanism by which bilirubin increased asthma risk was related to the peak level, then practices that limit maximum TSB levels might be effective in reducing asthma risk. However, even if that were the case, much of the attributable risk in the CPP occurred at levels far below those at which phototherapy would currently be considered. The increase starts at peak TSB levels above just 3.0 mg/dL.

On the other hand, if the mechanism is really an underlying genetic predisposition to high bilirubin levels and asthma, interventions at lower TSB levels will have no effect. This is an important distinction to make before physicians become more aggressive in treating hyperbilirubinemia in hopes of reducing the incidence of asthma. Although phototherapy is generally considered benign, large longitudinal studies examining its potential adverse effects are lacking. In addition, phototherapy can interfere with parent-child bonding and breastfeeding and could potentially increase costs because of longer hospitalizations.

The elucidation of risk factors for disease can be helpful for furthering our understanding of disease biology, supporting possible disease prevention, or both. In the counterfactual framework, we estimate the causal effect of an exposure as the difference in outcomes if everyone in the population were exposed compared with if no one were exposed. But for clinical or public health decisions, in which we try to prevent an outcome by altering exposure, how the exposure is altered is key. For exogenous exposures, such as those to treatments or toxic chemicals, the method of achieving the counterfactual exposure state is potentially straightforward—it may simply involve avoiding the treatment or chemical exposure. But when the risk factor of interest occurs naturally, such as a maximum TSB level in a newborn, knowing the mechanism by which it would be lowered is key to estimating the relevant causal effect (34). Potential interventions to reduce maximum TSB levels include greater use of infant formula, phototherapy, and medications such as heme oxygenase inhibitors. Because all of these interventions could plausibly increase the risk of asthma and/or have other significant adverse effects, it is vital that their effects be carefully studied before increasing their use in hopes of preventing asthma.

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