Hyperbilirubinemia, Phototherapy, and Childhood Asthma

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OBJECTIVES: Our aim was to quantify the associations of both hyperbilirubinemia and phototherapy with childhood asthma using a population-based cohort with total serum bilirubin (TSB) levels.

METHODS: Retrospective cohort study of infants born at ≥35 weeks’ gestation in the Kaiser Permanente Northern California health system (n = 109,212) from 2010 to 2014. Cox models were used to estimate hazard ratios (HRs) for a diagnosis of asthma.

RESULTS: In the study, 16.7% of infants had a maximum TSB level of ≥15 mg/dL, 4.5% of infants had a maximum TSB level of ≥18 mg/dL, and 11.5% of infants received phototherapy. Compared with children with a maximum TSB level of 3 to 5.9 mg/L, children with a TSB level of 9 to 11.9 mg/dL, 12 to 14.9 mg/dL, and 15 to 17.9 mg/dL were at an increased risk for asthma (HR: 1.22 [95% confidence interval (CI): 1.11–1.3], HR: 1.18 [95% CI: 1.08–1.29], and HR: 1.30 [95% CI: 1.18–1.43], respectively). Children with a TSB level of ≥18 mg/dL were not at an increased risk for asthma (HR: 1.04; 95% CI: 0.90–1.20). In propensity-adjusted analyses, phototherapy was not associated with asthma (HR: 1.07; 95% CI: 0.96–1.20).

CONCLUSIONS: Modest levels of hyperbilirubinemia were associated with an increased risk of asthma, but an association was not seen at higher levels. No dose-response relationship was seen. Using phototherapy to prevent infants from reaching these modest TSB levels is unlikely to be protective against asthma.

WHAT’S KNOWN ON THIS SUBJECT: Observational studies have revealed an association between hyperbilirubinemia and/or phototherapy and childhood asthma. In many studies, researchers have only used codes for hyperbilirubinemia or jaundice and have lacked the ability to distinguish between the effects of hyperbilirubinemia and its treatment.

WHAT THIS STUDY ADDS: By using actual bilirubin levels, modest levels of hyperbilirubinemia were associated with a slightly increased risk of asthma in a large modern cohort, but an association was not seen at higher levels. Phototherapy did not alter the risk of asthma.
The prevalence of childhood asthma has been increasing worldwide, and asthma is one of the most common childhood diseases, yet much remains to be elucidated concerning its etiology. There is clearly a genetic predisposition, and the interaction between the environmental pollutants and/or allergens, inflammatory mediators, and cellular response play a crucial role in its pathogenesis. Reactive oxygen species that are generated by both cellular metabolism and environmental pollutants result in oxidant injury and contribute to the severity and symptom exacerbation of asthma.

Observational studies have revealed an association between hyperbilirubinemia and/or phototherapy and childhood asthma. Using the Swedish birth registry, Asberg et al first reported an association between a diagnosis of icterus or history of phototherapy and hospitalizations for asthma after 2 years of age (adjusted odds ratio [aOR]: 1.27; 95% confidence interval [CI]: 1.08–1.50). The group confirmed their findings using an outcome of asthma, which was defined by receiving medications for asthma. Similarly, a Chinese (aOR: 1.64; 95% CI: 1.36–1.98) and Taiwanese study (adjusted hazard ratio [HR]: 1.21; 95% CI: 1.15–1.27) revealed an association between a diagnosis of neonatal jaundice and an inpatient or outpatient diagnosis of asthma later in childhood.

None of the authors of these studies analyzed actual bilirubin levels; all relied only on a diagnosis of jaundice. Because phototherapy is a primary treatment of neonatal jaundice, it is hard to distinguish the effects of phototherapy from those of jaundice. The only study in which actual bilirubin levels were included was an examination of data from the US Collaborative Perinatal Project; subjects were enrolled in 1959–1965, before the use of phototherapy.

Total serum bilirubin (TSB) levels were obtained on all infants at 36 to 60 hours after birth and repeated 24 hours later if the TSB level was >10 mg/dL. Compared with infants with a maximum TSB level of ≤3 mg/dL, infants with a maximum TSB level as low as 6.1 to 9 mg/dL were more likely to be diagnosed with asthma before age 7 years. Infants with a maximum TSB level of ≥15 mg/dL had the highest increased risk of asthma (aOR: 1.61; 95% CI: 1.04–2.08).

Our objective was to quantify the associations of both hyperbilirubinemia and phototherapy with childhood asthma, controlling for confounding using a large, modern, and population-based cohort and actual TSB levels.

**METHODS**

**Study Design**

We performed a retrospective cohort study as an extension of the Late Impact of Getting Hyperbilirubinemia or Phototherapy study. The Institutional Review Boards at Kaiser Permanente Northern California (KPNC) and the University of California, San Francisco, approved the study.

**Population**

The cohort included infants born at ≥35 weeks’ gestation at KPNC hospitals between January 1, 2010, and December 31, 2014. Only the 11 facilities that were employing universal bilirubin screening with TSB levels before discharge were included. To ensure full ascertainment of bilirubin levels, infants had to remain in the KPNC system during their entire birth hospitalization (n = 126,376). To assess asthma outcomes, we excluded children who did not remain in the health plan for at least 25 months after birth (n = 17,496). We excluded 332 children with no TSB levels. The final study cohort consisted of 109,212 children.

**Predictors**

**Bilirubin Measurement**

From existing KPNC laboratory databases, we obtained all TSB levels from an infant’s first month after birth using previously described methods. We excluded any TSB measurements for which a corresponding conjugated or direct bilirubin measurement constituted ≥50% of the TSB level. These infants represent a small and different population of infants and are also excluded from the American Academy of Pediatrics (AAP) guideline. TSB levels were obtained before discharge or if clinically indicated. Subsequent TSB testing was done at the discretion of the treating physicians. A bilirubin measurement was performed by using the Vitros BuBc Neonatal Bilirubin assay (Ortho Clinical Diagnostics, Raritan, NJ). In May 2012, Or thro Clinical Diagnostics adjusted the calibrator values for Vitros BuBc Slides, so we included an indicator variable for whether the TSB level was obtained before or after recalibration in analyses.

**Phototherapy**

We classified infants as having received inpatient phototherapy if they had either a phototherapy nursing flow sheet or both a procedure code and an order for phototherapy. Home phototherapy was determined from the KPNC durable medical equipment database.

**Additional Covariables**

From the KPNC electronic data sources, we abstracted covariates, including maternal age, maternal race and/or ethnicity, infant sex, gestational age, birth weight, 5-minute Apgar score, year, and hospital of birth, and the results of a direct antiglobulin test and glucose-6-phosphate dehydrogenase.
activity, if performed. A maternal history of asthma was defined as 2 asthma diagnoses (International Classification of Diseases, Ninth Revision diagnosis code 493.x) in the mother from any outpatient or inpatient encounter, separated by at least 30 days, occurring within 10 years before the birth of the infant (obtained from the KPNC Virtual Data Warehouse). We classified feeding during the birth hospitalization as exclusively breastfed, received 1 formula feeding, or received >1 formula feeding.

**Outcomes**

An occurrence of asthma was defined as a child having both (1) at least 2 asthma diagnoses from any outpatient or inpatient encounter, separated by at least 30 days, occurring after 2 years of age and (2) at least 2 asthma medication prescriptions in a 12-month period, separated by at least 30 days, prescribed after 2 years of age. Medications that were considered asthma medications were short- or long-acting β-agonists, inhaled corticosteroids, a combination inhaled corticosteroid and long-acting β-agonist, or a montelukast.

**Follow-up Time**

Length of follow-up varied in this study because some subjects left the KPNC health care system and follow-up began at birth (2010–2014) but ended in 2017 for all subjects. For purposes of quantifying incidence rates and using proportional hazards models, follow-up for each member of the cohort began at either age 2 years and ended at death, at the date when the individual met all criteria for asthma (2 asthma diagnoses and 2 medication prescriptions), or at the last follow-up date, which was defined as the last day of the last calendar month of coverage by the KPNC health plan or the last encounter date through April 30, 2017, whichever came later.

**Statistical Analysis**

We calculated crude incidence rates by dividing asthma cases by person years of follow-up, and we calculated CIs for comparing incidence rate ratios (IRRs) using exact binomial calculations. We used Cox proportional hazards models to evaluate the independent associations between hyperbilirubinemia and asthma and phototherapy and asthma, adjusting for potential confounders. We investigated which variables were independently associated with asthma in models that included maximum TSB levels and phototherapy. Covariables with a significance value of $P < .05$ were included in the final model. In addition to traditional models, we used a phototherapy propensity score among infants who had a TSB level within 3 mg/dL of the AAP phototherapy threshold, as previously described. We categorized propensity scores for phototherapy by decile. In propensity-adjusted analyses we controlled for measured confounding variables by creating a model for the probability of exposure (in this case, phototherapy) and then controlled for that probability. This allowed us to adjust for TSB levels before but not after phototherapy, thus allowing us to investigate whether phototherapy might reduce the risk of asthma by preventing hyperbilirubinemia.

We performed all analyses using Stata version 15 (Stata Corp, College Station, TX).

**RESULTS**

Characteristics of the study cohort by asthma status are shown in Table 1. As expected, African American children, children of mothers with a history of asthma, and infants of lower gestational age were overrepresented in the asthma group. Infants who were exclusively breastfed during the birth hospitalization were underrepresented in the asthma group. Infants who received phototherapy were overrepresented in the asthma group.

Of the 109212 children in the cohort, 16.7% (18205) had a maximum TSB level of ≥15 mg/dL, and 4.7% (4865) had a maximum TSB level of ≥18 mg/dL. Phototherapy was administered to 11.5% (12533) of the children. The majority of children who were treated received inpatient phototherapy (8.9%), whereas a minority (2.5%) received only home phototherapy. Children were managed for a total of 263967 person years after age 2 years. The mean age at the last follow-up was 4.4 (SD: 1.5) years. In the study, 4854 (4.4%) children met the criteria for asthma (incidence rate: 18.4 per 1000 person years). The mean age to achieving criteria for an asthma diagnosis was 3.6 (SD: 1.1) years old.

Asthma cases, the cumulative incidence of asthma, the incidence rate, and IRRs by maximum TSB level category are shown in Table 2. Although incidence rates for asthma increased significantly for maximum TSB levels between 9 and 17.9 mg/dL compared with maximum TSB levels between 3 and 5.9 mg/dL, there was not a significant increase in incidence rates for asthma in children with maximum TSB levels of ≥18 mg/dL. Figure 1 includes the asthma incidence rate by maximum TSB level. No clear relationship is present.

For the Cox proportional hazards models, sex, maternal history of asthma, cesarean delivery, birth hospitalization length of stay >7 days, recalibration, race, maternal age, gestational age, birth facility, birth year, and feeding type during the birth hospitalization were included in the final model. In the final model, phototherapy was not associated with asthma (HR: 1.01; 95%
CI: 0.92–1.11; Table 3). Maximum TSB levels between 9 and 17.9 mg/dL were associated with an elevated HR for asthma; however, there was no association between a TSB level of ≥18 mg/dL and asthma. In our cohort, 88% of those who met criteria for an asthma diagnosis, met criteria before 5 years of age. Limiting the analysis to individuals with at least 5 years of follow-up yielded similar associations with TSB levels. In additional analyses, we separated home phototherapy and inpatient phototherapy. Neither was associated with asthma (HR: 0.98 [95% CI: 0.86–1.16] for inpatient phototherapy; HR: 1.01 [95% CI: 0.85–1.19] for home phototherapy). Lastly, restricting the model to infants with a positive Coombs test revealed higher TSB levels to be protective.

In the subset of infants with a TSB level within 3 mg/dL of the AAP phototherapy threshold before any treatment with phototherapy (n = 28,290), phototherapy was not associated with childhood asthma (HR: 1.07; 95% CI: 0.96–1.20; controlling for the propensity to receive phototherapy).

**DISCUSSION**

In a large modern cohort, with TSB levels for all subjects, we found that infants with moderately elevated maximum TSB levels (9–17.9 mg/dL) were more likely to develop asthma later in childhood. This association did not persist for infants with maximum TSB levels of ≥18 mg/dL. We found no association between phototherapy and asthma when adjusting for the maximum TSB level or in analyses when adjusting for a propensity to receive phototherapy.

Although we have confirmed an association between moderately elevated bilirubin levels at birth and the development of asthma later in childhood, the question is if the association is causal. There is undoubtedly consistency because this association has now been seen in diverse populations in Sweden, Taiwan, China, and now in a historic and modern cohort in the United States. The strength of the association in the aforementioned studies ranged from aORs of 1.37 to 1.64. The strength of the association in our study was attenuated, which may be secondary to our controlling for other important predictors, such as a history of maternal asthma and the more specific definition of asthma that we used.

Is there any biological plausibility for why hyperbilirubinemia or phototherapy may result in asthma?
In vivo, bilirubin plays an important role as an antioxidant; however, at higher levels (>20 mg/dL) bilirubin fails to provide protection. Perhaps a resultant oxidant–antioxidant imbalance may result in airway inflammation, with the development of asthma later in life. Our results do not support this mechanism because it would predict the risk to be greatest in children with the highest maximum TSB level. This rationale also requires that a brief exposure early in life would result in enough injury that would predispose an individual to asthma many years later, which seems unlikely.

Others have suggested that bilirubin may influence the immune system. Unconjugated bilirubin may shift the T helper (Th) cell balance of Th1 to Th2 toward the Th2 phenotype through an inhibition of interleukin-2 production. A Th2 predominance had been associated with the development of allergy and asthma. Interleukin-2 is essential for the development and maintenance of T regulatory cells, which play an important role in regulating immunologic processes in peripheral tolerance to allergens. The exposure is brief, but perhaps an alteration in cytokine production with hyperbilirubinemia could favor intolerance at a critical time in immune system development.

However, our data did not reveal a biological gradient or dose response of maximum bilirubin level and the risk of asthma. In fact, as maximum TSB levels increased, we saw a fall in the incidence of asthma after a maximum TSB level of 16 mg/dL. In comparison, the Collaborative Perinatal Project revealed a trend of an increasing risk of asthma with higher TSB levels at 48 hours and maximum TSB levels, with the highest risk in children with a TSB level of >15 mg/dL. However, we were able to look at more gradations >15 mg/dL rather than group all the individuals together. Although the Collaborative Perinatal Project had 901 infants with a TSB level of >15 mg/dL, we had 13340 infants with a maximum TSB level of 15 to 17.9 mg/dL and another 4865 infants with a maximum TSB level of 18 to 20.9 mg/dL.

If hyperbilirubinemia is implicated in the development of asthma, could the effect be ameliorated or prevented by treatment? No differences in the risk of asthma were seen between infants who were and were not treated with phototherapy. This may not fully answer the question, however, because the increased risk was seen at maximum TSB levels as low as 9 mg/dL. Many infants may have already reached TSB levels that are associated with an increased risk of asthma but are well below AAP recommended thresholds for phototherapy. Because there was no dose-response relationship between maximum TSB levels and asthma risk, preventing higher levels through phototherapy may not have any effect on asthma risk unless started at much lower thresholds.

The most likely alternative explanation for this association is a confounder, such as a genetic predisposition to both moderate hyperbilirubinemia and asthma. A potential example is polymorphisms in the glutathione S-transferase (GST) gene. Mutations have been linked to

<table>
<thead>
<tr>
<th>TSB, mg/dL</th>
<th>No. Infants</th>
<th>Asthma Cases</th>
<th>Cumulative Incidence of Asthma, %</th>
<th>Incidence Per 1000 Person Years</th>
<th>IRR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>5225</td>
<td>205</td>
<td>3.9</td>
<td>16.69</td>
<td>1.01 (0.87–1.18)</td>
<td>.9</td>
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<td>3–5.9</td>
<td>27170</td>
<td>1004</td>
<td>3.7</td>
<td>16.46</td>
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<td>—</td>
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<tr>
<td>6–8.9</td>
<td>25738</td>
<td>1059</td>
<td>4.1</td>
<td>17.42</td>
<td>1.06 (0.97–1.15)</td>
<td>.2</td>
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<td>9–11.9</td>
<td>15624</td>
<td>757</td>
<td>4.8</td>
<td>20.02</td>
<td>1.22 (1.11–1.34)</td>
<td>&lt;.001</td>
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<tr>
<td>12–14.9</td>
<td>17252</td>
<td>849</td>
<td>4.9</td>
<td>19.45</td>
<td>1.18 (1.08–1.29)</td>
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</tr>
<tr>
<td>15–17.9</td>
<td>13340</td>
<td>752</td>
<td>5.6</td>
<td>21.41</td>
<td>1.30 (1.18–1.43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥18</td>
<td>4865</td>
<td>228</td>
<td>4.7</td>
<td>17.15</td>
<td>1.04 (0.90–1.20)</td>
<td>.9</td>
</tr>
</tbody>
</table>

*—, not applicable.*
both neonatal hyperbilirubinemia and asthma.\textsuperscript{39,40} 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.\textsuperscript{48} Neonates with the GSTM1-null genotype have higher TSB levels compared with those with the wild phenotype.\textsuperscript{39,40} GST is also involved in cytoprotection from byproducts of oxidative stress.\textsuperscript{49} GST is widely expressed in human airways and may play a role in modifying the risk of allergic response to environmental pollutants.\textsuperscript{50-52}

Multiple meta-analyses of the association between GST genes and asthma have had conflicting results and have been hampered by study heterogeneity.\textsuperscript{42-45} The polymorphism is not rare, which adds to the plausibility; the frequency of the GSTM1-null genotype is \(\sim\)50% in white individuals and \(\sim\)20% in African Americans.\textsuperscript{53}

A possible explanation to why an association was seen between moderate hyperbilirubinemia and asthma and not a more severe hyperbilirubinemia may relate to the etiology of hyperbilirubinemia. Moderate hyperbilirubinemia may be associated with polymorphisms in the GST gene, whereas a more severe hyperbilirubinemia may be seen more commonly with etiologies, such as ABO incompatibility, glucose-6-phosphate dehydrogenase deficiency, or sepsis. As a result, a common gene polymorphism that leads to moderate hyperbilirubinemia may be the etiology of hyperbilirubinemia in a greater percentage of infants with moderate hyperbilirubinemia, whereas in infants with severe hyperbilirubinemia, other etiologies are more common. Another possibility may be that there are 2 conflicting mechanisms. Bilirubin is both causal and protective at different levels, and at a level of \(>18\) mg/dL, the protective mechanism overcomes the causal one.

Further lessening the case for causality, in both this study and past studies, TSB levels of \(<10\) mg/dL were associated with asthma. The low bilirubin levels make it more plausible that it is not the bilirubin itself that is increasing the risk of asthma but rather a confounder.

A finding in our results that deserves further examination was that any formula feeding, even a single formula feeding during the birth hospitalization, was associated with asthma. The extent to which formula feeding during the birth hospitalization serves as simply an indication of formula feeding in childhood asthma. The extent to which formula feeding during the birth hospitalization serves as simply an indication of formula feeding in the subsequent months is unknown.

A major strength of our study is the large, modern, and diverse cohort. Homogenous populations were used in many of the previous studies, whereas in our cohort, there was representation of many races and ethnicities, increasing its generalizability. For our main predictors, we had actual bilirubin levels rather than codes for jaundice, and we used both orders and flow sheets for phototherapy rather than administrative codes. Additionally, our outcome variable was specific; multiple encounters were used with diagnostic codes in conjunction with

### TABLE 3 Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum TSB level, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>1.00 (0.86–1.16)</td>
<td>.88</td>
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<tr>
<td>3–5.9</td>
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<tr>
<td>6–8.9</td>
<td>1.04 (0.96–1.14)</td>
<td>.3</td>
</tr>
<tr>
<td>9–11.9</td>
<td>1.14 (1.04–1.26)</td>
<td>.007</td>
</tr>
<tr>
<td>12–14.9</td>
<td>1.12 (1.02–1.24)</td>
<td>.02</td>
</tr>
<tr>
<td>15–17.9</td>
<td>1.22 (1.10–1.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥18</td>
<td>0.90 (0.84–1.16)</td>
<td>.9</td>
</tr>
<tr>
<td>Any phototherapy</td>
<td>1.01 (0.92–1.11)</td>
<td>.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.61 (1.52–1.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal history of asthma</td>
<td>2.34 (2.17–2.52)</td>
<td>&lt;.001</td>
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<tr>
<td>Cesarean delivery</td>
<td>1.01 (0.94–1.08)</td>
<td>.839</td>
</tr>
<tr>
<td>Birth hospitalization length of stay &gt;7 d</td>
<td>1.51 (1.26–1.17)</td>
<td>&lt;.001</td>
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<tr>
<td>Recalibration</td>
<td>1.03 (0.91–1.17)</td>
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<tr>
<td>Race</td>
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<tr>
<td>Asian American</td>
<td>1.13 (1.04–1.23)</td>
<td>.005</td>
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<tr>
<td>African American</td>
<td>1.95 (1.76–2.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.25 (1.16–1.36)</td>
<td>&lt;.001</td>
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<tr>
<td>White</td>
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</tr>
<tr>
<td>Other</td>
<td>1.11 (0.99–1.24)</td>
<td>.080</td>
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<tr>
<td>Maternal age, y</td>
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<tr>
<td>&lt;20</td>
<td>1.17 (1.01–1.36)</td>
<td>.038</td>
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<td>20–29</td>
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<tr>
<td>30–39</td>
<td>1.04 (0.97–1.10)</td>
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<tr>
<td>≥40</td>
<td>0.95 (0.81–1.07)</td>
<td>.281</td>
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<tr>
<td>Gestational age, wk</td>
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<td>35</td>
<td>1.15 (0.93–1.37)</td>
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</tr>
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<td>36</td>
<td>1.28 (1.11–1.48)</td>
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<td>37</td>
<td>1.10 (0.98–1.23)</td>
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<tr>
<td>38</td>
<td>1.05 (0.96–1.15)</td>
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<td>39</td>
<td>1.00 (0.93–1.08)</td>
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<tr>
<td>≥41</td>
<td>0.94 (0.84–1.04)</td>
<td>.240</td>
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<tr>
<td>Birth hospitalization feeding</td>
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</tr>
<tr>
<td>Exclusive breast milk</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1 formula feed</td>
<td>1.25 (1.10–1.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 formula feed</td>
<td>1.17 (1.10–1.25)</td>
<td>&lt;.001</td>
</tr>
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</table>

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* Adjusted for facility and birth year.
pharmacy data that indicated the use of asthma medications. We were able to control for a large number of possible confounding variables, including infant feeding type (breast milk versus formula) during the birth hospitalization, maternal history of asthma, and gestational age. Using a modern cohort, we were limited by differential follow-up, although this was accounted for in our analyses by using Cox models.

There is a possible underdiagnosis of asthma in those infants who were born in the later birth years because of a more limited follow-up. However, when we limited the analysis to those with at least 5 years of follow-up, the same associations persisted.

Lastly, all bilirubin measurements were obtained as clinically indicated. Especially for infants with lower maximum TSB levels, an infant’s true maximum TSB level may have been higher but unmeasured because repeat testing may not have been clinically indicated if there was a low likelihood of reaching phototherapy treatment levels. However, this misclassification would have made it more difficult to detect an association in the study.

CONCLUSIONS
An association between modest levels of hyperbilirubinemia and asthma exists. The association is unlikely to be causal because no dose-response relationship was seen, with the highest levels of hyperbilirubinemia not being associated with asthma. A confounder, such as a genetic polymorphism, is more likely associated with both asthma and modestly decreased bilirubin conjugation. Phototherapy did not alter the risk of asthma. Using phototherapy to prevent infants from reaching these modest TSB levels is unlikely to be useful and would require phototherapy use in ~50% of the birth population.

ABBREVIATIONS
AAP: American Academy of Pediatrics
aOR: adjusted odds ratio
CI: confidence interval
HR: hazard ratio
IRR: incidence rate ratio
KPNC: Kaiser Permanente Northern California
Th: T helper
Th2: T helper 2
TSB: total serum bilirubin

REFERENCES

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by grant 8010520618 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The funder played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.


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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-0662 originally published online September 12, 2018;

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