



Original Contribution

Neonatal Bilirubin Levels and Childhood Asthma in the US Collaborative Perinatal Project, 1959–1965

Lisu Huang, Yixiao Bao, Zongli Xu, Xiaoping Lei, Yan Chen, Yongjun Zhang, and Jun Zhang*

* Correspondence to Dr. Jun Zhang, MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, 1665 Kong Jiang Road, Shanghai, China 200092 (e-mail: junjimzhang@gmail.com).

Initially submitted January 24, 2013; accepted for publication June 11, 2013.

Evidence shows that asthma originates in early life. Studies have found that phototherapy and/or neonatal jaundice may be associated with asthma. We investigated the association between neonatal bilirubin levels and childhood asthma without phototherapy intervention in the Collaborative Perinatal Project, a multicenter prospective cohort study conducted in the United States from 1959 to 1965. A total of 54,795 livebirths were included, and 40,063 children were followed up until 7 years of age or older. Total serum bilirubin (TSB) levels were examined at 48 hours postpartum in newborns with birthweights of 2,250 g or more. Information on asthma and other diseases through age 7 years was summarized and confirmed by a group of pediatricians and child neurologists. Among 28,807 term infants, the overall prevalence of asthma was 5.26%. Risks of asthma increased with both maximum TSB levels and TSB levels at 48 hours postpartum (P for trend < 0.01). Neonatal maximum TSB levels greater than 15 mg/dL were associated with a 61% increase in the risk of childhood asthma (odds ratio = 1.61, 95% confidence interval: 1.04, 2.08) after adjustment for confounders. In this prospective cohort study of infants born at a time when phototherapy was unavailable, neonatal hyperbilirubinemia was associated with an increased risk of childhood asthma.

asthma; bilirubin; immaturity; perinatal exposure; phototherapy

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

Editor's note: An invited commentary on this article appears on page 000.

Asthma is one of the most common chronic diseases, affecting nearly 25 million Americans. Children aged 0–17 years have a higher prevalence of asthma (9.5%) than do adults aged 18 years and older (7.7%) (1). There is widespread concern that the incidence of asthma is still rising in developed countries (2). However, the causes of asthma are not fully understood. More and more evidence shows that asthma has its origins in early life or even in utero (3, 4). Several perinatal factors have been consistently suggested to be associated with asthma, such as maternal smoking, young maternal age, preterm birth, and low birthweight (5).

More than half (50%–60%) of neonates develop visible jaundice due to elevated bilirubin concentration in the first

week of life (6). Although most cases of neonatal jaundice are physiological, the long-term effects of neonatal bilirubin exposure on children and even adults remain controversial (7). Several studies found that phototherapy and/or neonatal jaundice was associated with asthma. The odds ratios ranged from 1.30 (95% confidence interval (CI): 1.16, 1.47) to 1.64 (95% CI: 1.36, 1.98) after adjustment for confounders (8, 9). In these studies, neonatal jaundice was defined in children who underwent phototherapy according to data in the national register system but for whom information on bilirubin levels was unavailable. Because phototherapy is a primary treatment for neonatal jaundice, it may be difficult to separate phototherapy from neonatal hyperbilirubinemia in current clinical practice. Thus, it remains unclear whether neonatal jaundice, phototherapy, or both are associated with an increased risk of asthma. We examined the association between neonatal bilirubin levels and childhood asthma without the

complication of phototherapy in the Collaborative Perinatal Project (CPP), a large prospective study of births occurring in the United States in 1959–1965, when phototherapy had yet to be applied clinically (10).

MATERIALS AND METHODS

Study population

The CPP was a prospective study that recruited 46,021 women with 56,990 pregnancies at 12 centers in the United States from 1959 to 1965. During the 7-year study period, 18% of participants had more than 1 birth. Children were followed with detailed assessments of neurological, neurosensory, and cognitive development, as well as general health and physical growth at 8 months and 1, 3, 4, and 7 years of age. A detailed description of the study has been provided

elsewhere (11). We included 54,795 livebirths. Among 53,647 singletons, 74.7% ($n = 40,063$) were followed until 7 years of age (Figure 1). Preterm (gestational age <37 weeks) and low-birthweight infants (birthweight <2,500 g) were excluded, as were children with unknown bilirubin levels ($n = 1,423$). We further excluded infants who had experienced neonatal respiratory diseases, because these children may have higher bilirubin levels and a potentially a higher risk of asthma (12). Finally, 28,807 term infants remained for analysis, all of whom had information on asthma.

Bilirubin measurements

Bilirubin was measured by the diazo method in 11 of the 12 centers and by direct spectrophotometry in the other center. The coefficient of variation of standard specimens among

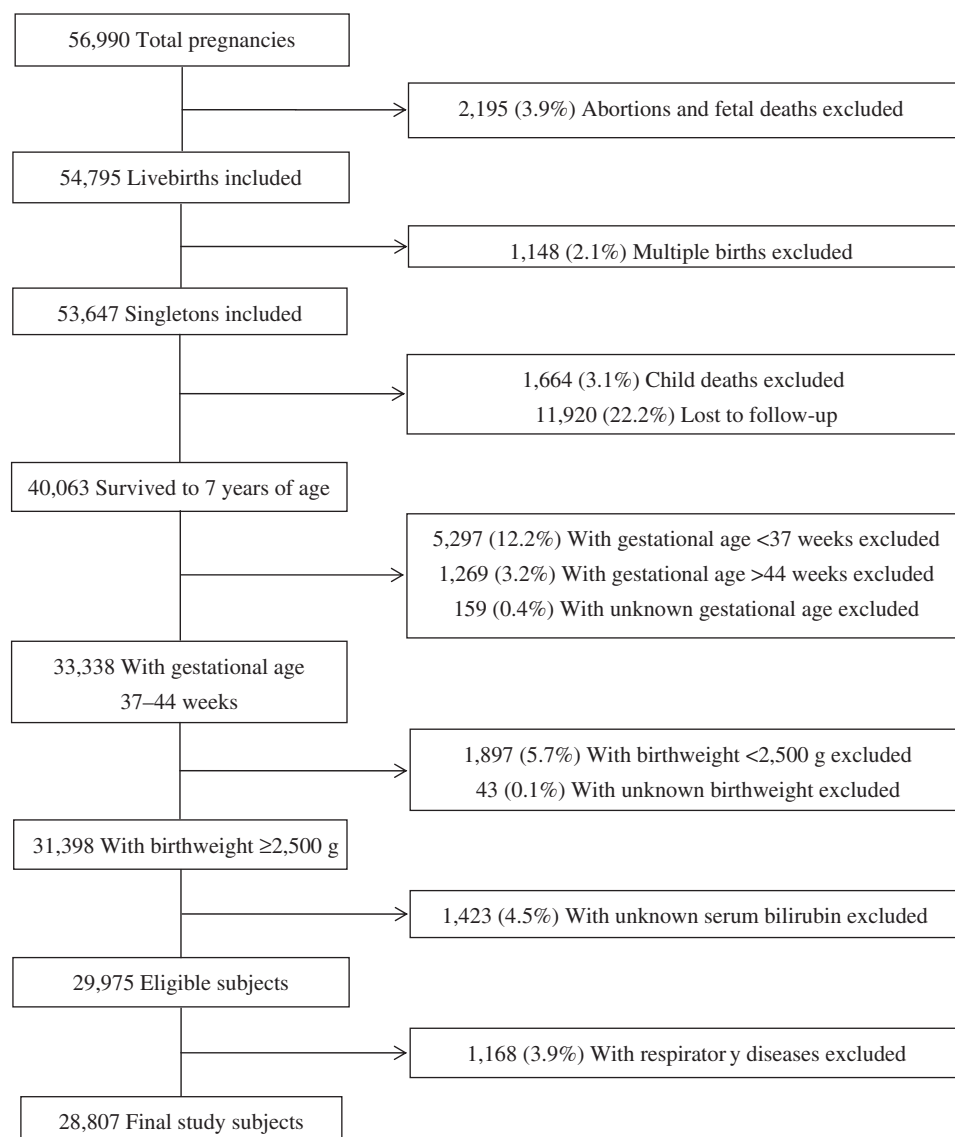


Figure 1. Study population flow chart, Collaborative Perinatal Project, United States, 1959–1965.

CPP laboratories was approximately 10%, and the intralaboratory coefficient of variation was approximately 2% (13). For all infants with birthweights of 2,250 g or more, the study protocol required measuring total serum bilirubin (TSB) levels at 36–60 hours postpartum (as close to 48 hours postpartum as possible). If a TSB level was higher than 10 mg/dL, a second test was obtained 24 hours later. If the second TSB level exceeded 10 mg/dL, a third test was required at 4–5 days of age. Additional bilirubin measurements were obtained at the discretion of physicians at each study site. We used the 48-hour TSB and maximum TSB data in this analysis.

Diagnosis of asthma

Detailed information on child health was collected, and various physical examinations were performed in each visit at 8 months and 1, 3, 4, and 7 years of age (14). All recorded health and disease information for each child through the age of 7 years was reviewed, summarized, and confirmed by a group of pediatricians and pediatric neurologists. Asthma diagnosis and related information in the current analysis was extracted mainly from the summarized data file. The diagnosis of asthma was recoded as “suspected,” “definite,” or “history only” according to the medical history at 1 year and 7 or 8 years of age. We used “definite” asthma as an event in this study. This classification scheme was consistent with a previous study of asthma that used the same data (15). A total of 169 subjects who were diagnosed with asthma at 1 year of age and without asthma by 7 years of age were recoded as “nonasthma.”

Confounders

Prenatal factors that may affect the relationship between neonatal bilirubin level and asthma were chosen as potential confounders according to previous literature (16). Maternal characteristics included maternal age at delivery (<20, 20–29, 30–39, or ≥40 years), marital status at pregnancy (no/yes); race (white, black, or other); educational level (<9, 10–12, or >12 years); number of previous deliveries (0, 1, or ≥2); smoking during pregnancy (0, 1–9, or ≥10 cigarettes per day), and maternal allergic diseases (no/yes). Child characteristics included sex, Apgar score at 5 minutes (0–6 or 7–10), mode of delivery (vaginal, assisted vaginal, or cesarean), birthweight (2,500–2,999, 3,000–3,499, 3,500–3,999, or ≥4,000 g), and breastfeeding (no/yes). Data on gestational age were based on the last menstrual period.

Statistical analysis

We first examined the differences in maternal and child baseline characteristics between children with and without asthma by using the χ^2 test. We plotted separately the prevalence rates of asthma by the level of TSB at 48 hours postpartum and by maximum TSB level. Smoothed curves using the locally weighted scatterplot smoothing method were added. We conducted a trend analysis to evaluate the exposure-response relationship between bilirubin level and prevalence of childhood asthma with adjustment for confounders (17).

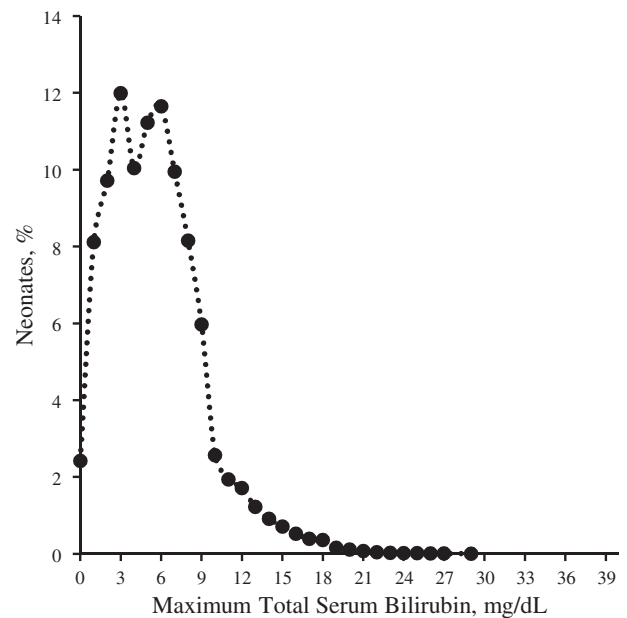


Figure 2. Prevalence distribution of neonates by maximum total serum bilirubin levels, Collaborative Perinatal Project, United States, 1959–1965.

The distribution of maximum TSB levels was left skewed with dual modality (Figure 2) and could not be transformed to a normal distribution. We therefore categorized the TSB data in tertiles with cutoff points of 3 mg/dL (cumulative percent: 32.2%) and 6 mg/dL (cumulative percent: 64.9%). Because TSB levels lower than 9 mg/dL at 48 hours postpartum would put a child in the low-risk zone with no need for phototherapy, and because phototherapy would not begin until TSB levels reached 15 mg/dL (18), the levels of bilirubin were further categorized into the following 5 groups: ≤3, 3.1–6, 6.1–9, 9.1–15, and >15 mg/dL. Children from the same family share similar genetic and home environments; thus, we used the generalized estimating equation model to correct for intracluster correlation with the GENMOD procedure in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) with family number as the repeated subject. We started the model with the association of asthma and bilirubin level, and each potential confounder was then put into the model, 1 at a time. A variable was considered a confounder if it changed the β coefficient of the main effect by more than 10%. Eventually, maternal race, sex, gestational age, and study center were included in the analysis.

RESULTS

Maternal and child characteristics of this study population are presented by asthma status in Table 1. There were no significant differences between asthma and nonasthma groups in most of the characteristics considered. Both asthma and nonasthma groups were predominantly vaginal deliveries to married, non-smoking mothers. The asthma group had a higher proportion of allergic mothers, male infants, and black race ($P < 0.05$).

Table 1. Maternal and Child Characteristics by Asthma Status in the Collaborative Perinatal Project, United States, 1959–1965

Characteristic	Nonasthma (n = 27,293)		Asthma (n = 1,514)		P Value ^a
	No.	%	No.	%	
Maternal race					<0.01
White	14,018	51.4	645	42.6	
Black	12,323	45.2	785	51.9	
Other	952	3.5	84	5.6	
Maternal age, years					0.33
<20	5,998	22.0	351	23.2	
20–29	15,767	57.8	838	55.4	
30–39	5,046	18.5	297	19.6	
≥40	482	1.8	28	1.9	
Married at pregnancy	21,485	78.7	1,151	76.0	0.04
Maternal education					0.34
Less than high school	7,455	27.3	439	29.0	
High school	16,344	59.9	890	58.8	
College and above	3,494	12.8	185	12.2	
Smoking during pregnancy					0.27
Nonsmoker (0 cigarettes/day)	14,824	54.3	810	53.5	
Light smoker (1–9 cigarettes/day)	7,878	28.9	456	30.1	
Heavy smoker (≥10 cigarettes/day)	4,425	16.2	244	16.1	
Maternal allergic diseases	3,039	11.1	203	13.4	<0.01
Parity					0.09
0	7,921	29.0	469	31.0	
1	6,118	22.4	355	23.5	
≥2	13,199	48.4	685	45.2	
Mode of delivery					0.58
Vaginal	25,363	92.9	1,407	92.9	
Assisted vaginal	548	2.0	35	2.3	
Cesarean	1,361	5.0	72	4.8	

Table continues

There were 1,514 asthmatic children among the 28,807 subjects, with an overall prevalence of 5.26%. A total of 88.6% of neonates had maximum bilirubin levels lower than 9 mg/dL, and 97.6% of neonates had levels lower than 15 mg/dL (Table 2). Figure 3 shows that the prevalence of asthma increased significantly with both maximum TSB level and TSB level at 48 hours postpartum after adjustment for confounders ($P < 0.01$). Children with TSB levels higher than 15 mg/dL had the highest prevalence of asthma (8.01% for TSB at 48 hours postpartum and 7.99% for maximum TSB). The prevalence of asthma was associated with increased maximum TSB level, and the odds ratios in the groups of ≤3, 3.1–6, 6.1–9, 9.1–15, and >15 mg/dL were 1.00, 1.08, 1.22, 1.19, and 1.61, respectively, after adjustment

Table 1. Continued

Characteristic	Nonasthma (n = 27,293)		Asthma (n = 1,514)		P Value ^a
	No.	%	No.	%	
Birthweight, g					0.44
2,500–2,999	6,945	25.5	389	25.7	
3,000–3,499	12,221	44.8	701	46.3	
3,500–3,999	6,469	23.7	332	21.9	
≥4,000	1,658	6.1	92	6.1	
Gestational age, weeks					0.13
37	1,646	6.0	104	6.9	
38	3,040	11.1	194	12.8	
39	5,400	19.8	314	20.7	
40	6,860	25.1	338	22.3	
41	5,421	19.9	305	20.3	
42	2,922	10.7	151	10.0	
43	1,306	4.8	71	4.7	
44	698	2.6	37	2.4	
Male sex	13,785	50.5	975	64.4	<0.01
Apgar score of 0–6 at 5 minutes	851	3.1	47	3.1	0.80
Breastfeeding	4,766	17.5	243	16.1	0.25
Indirect Coombs' test positive ^b	713	2.6	44	2.9	0.78
Exchange transfusion ^c	251	0.9	15	1.0	0.77

^a P values were determined by χ^2 test.^b Indirect Coombs' test positive detects antibodies against red blood cells that are present unbound in the patient's serum.^c Medical treatment in which apheresis is used to remove patient's red blood cells or platelets and replace them with transfused blood products.

for maternal race, sex, gestational age (by week), and study center (Web Tables 1 and 2, available at <http://aje.oxfordjournals.org/>).

DISCUSSION

Neonatal hyperbilirubinemia and asthma are frequently encountered in children. In the CPP, we found that, without the complication of phototherapy, the risks of asthma increased with both maximum TSB level and TSB level at 48 hours postpartum (P for trend < 0.01). Neonatal maximum TSB levels greater than 15 mg/dL were associated with a 61% increase in the risk of childhood asthma (odds ratio = 1.61, 95% CI: 1.04, 2.08) after adjustment for confounding variables.

To the best of our knowledge, there are only 3 articles published on this topic (8, 9, 19). Bu using data from the Swedish Hospital Discharge Register, Aspberg et al. (19) first reported the association between neonatal jaundice (defined as neonates who experienced phototherapy) and hospitalized childhood asthma (odds ratio = 1.27, 95% CI: 1.08, 1.50). In a

Table 2. Prevalence of Asthma by TSB Level at 48 Hours Postpartum and Maximum TSB Level and Odds Ratios in the Collaborative Perinatal Project, United States, 1959–1965

TSB, mg/dL	No. (Total <i>n</i> = 28,807)	No. of Asthma Cases (Total <i>n</i> = 1,514)	Prevalence of Asthma, % ^a	Crude Analysis		Adjusted Analysis ^b		Trend Analysis ^c	
				OR	95% CI	Adjusted OR	95% CI	<i>P</i> Value	Adjusted <i>P</i> Value
48-Hour level								0.0045	0.0093
≤3	5,945	286	4.81	1.00	Referent	1.00	Referent		
3.1–6	9,754	490	5.02	1.05	0.85, 1.38	1.07	0.92, 1.26		
6.1–9	8,747	492	5.62	1.19	1.05, 1.36	1.23	1.05, 1.44		
9.1–15	4,089	224	5.48	1.15	1.03, 1.28	1.17	1.02, 1.33		
>15	272	22	8.09	1.68	1.11, 2.25	1.59	0.89, 2.30		
Maximum level								0.0022	0.0078
≤3	5,792	269	4.64	1.00	Referent	1.00	Referent		
3.1–6	9,572	477	4.98	1.08	0.91, 1.25	1.08	0.93, 1.27		
6.1–9	8,443	475	5.63	1.20	1.15, 1.82	1.22	1.04, 1.42		
9.1–15	4,099	221	5.39	1.17	0.96, 1.42	1.19	0.91, 1.46		
>15	901	72	7.99	1.70	1.07, 2.45	1.61	1.04, 2.08		

Abbreviations: CI: confidence interval; OR, odds ratio; TSB, total serum bilirubin.

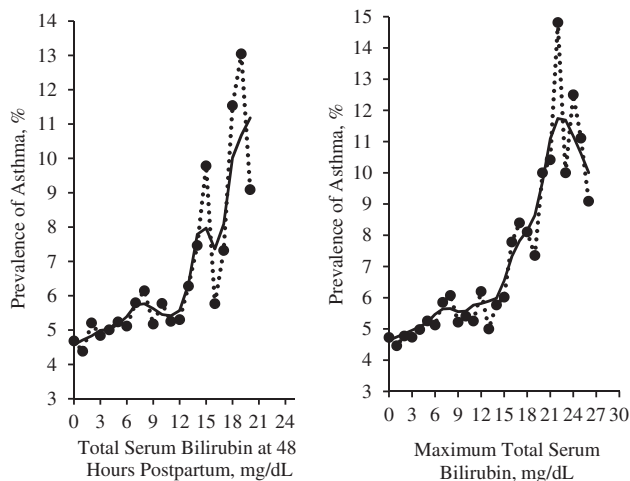
^a Overall prevalence of asthma = 5.26%.^b Generalized estimating equation model adjusted for maternal race, sex, gestational age, and study center with family number as repeated subject.^c Trend analysis adjusted for maternal race, sex, gestational age, and study center.

subsequent analysis based on data in the Swedish Prescribed Drug Register (8), the authors confirmed that phototherapy/neonatal jaundice was associated with the use of antiasthma drugs before 12 years of age (odds ratio = 1.30, 95% CI: 1.16, 1.47). In a recent retrospective study, Ku et al. (9) showed a

similar relationship between neonatal jaundice and asthma (odds ratio = 1.64, 95% CI: 1.36, 1.98).

All subjects in these studies were exposed to both neonatal jaundice and phototherapy. In addition, the diagnosis of neonatal jaundice was obtained from data in hospital discharge systems without specific values of bilirubin or timing of the measurements, which may have resulted in a certain degree of misclassification. Nonetheless, the magnitude of the relationship between neonatal jaundice and asthma in previous studies was surprisingly similar to our finding, suggesting that this association is less likely to be spurious. Furthermore, judging by the magnitude of the relationship between our results and previous studies, the interaction between neonatal icterus and phototherapy is less likely. Given that phototherapy was not used in our subjects, our study indicates that jaundice, not phototherapy, is associated with asthma. However, the underlying biological mechanisms remain unknown.

Physiological neonatal hyperbilirubinemia, especially in preterm infants, is caused mainly by increased bilirubin production (due to both relative polycythemia and shorter red blood cell lifespan), decreased clearance (due to decreased hepatic uptake and conjugation), and increased enterohepatic circulation (20). It has been found that neonates born at 37 weeks were 4 times more likely than those born at 40 weeks to have a bilirubin level greater than 13 mg/dL (21). This immaturity at birth is also associated with decreased childhood lung function (22). Moreover, poor enteral intake and delayed stooling in immature infants may alter intestinal flora, which may also be related to both hyperbilirubinemia

**Figure 3.** Prevalence of asthma by total serum bilirubin level, Collaborative Perinatal Project, United States, 1959–1965. Total serum bilirubin level at 48 hours postpartum (left panel) and maximum total serum bilirubin (right panel).

and asthma (23). Thus, it is critical to control for gestational age in examining the association between bilirubin level and asthma.

Bilirubin levels vary even in neonates of the same gestational age. Genetic polymorphisms of certain enzymes, such as uridine diphosphate glucuronyltransferase and glutathione S-transferase (GST), have been suggested to be associated with hyperbilirubinemia (24, 25). For example, GSTs, including *GSTM1*, *GSTT1*, and *GSTP1*, participate in binding to nonsubstrate ligands such as bilirubin. Neonates with the *GSTM1* null genotype are at high risk of developing hyperbilirubinemia (26). Genetic variations of GSTs were also associated with the ability to handle oxidative stress, which was considered an important pathological process in asthma. It has been found that histamine and immunoglobulin E responses to air pollution oxidants and allergens were increased in *GSTM1* null genotypes (27, 28). More efforts are necessary to examine genetic predisposition in the association between hyperbilirubinemia and asthma in future studies.

Bilirubin itself may affect the development of the immune system, as well. One study showed that intracellular accumulation of unconjugated bilirubin inhibits the production of interleukin-2 (29), which may cause a T-helper type 1/T-helper type 2 cytokine imbalance and immunoglobulin E class switch. Changes in cytokine profile as a response to neonatal exposures may lead to asthma and allergic diseases later in childhood (30).

Strengths and limitations

Our study has several strengths. As the largest prospective birth cohort study in the United States, the CPP was carefully conducted with a high long-term follow-up rate (mean = 88%) (11). In this study, serum bilirubin levels were assessed in newborns with birthweights of 2,250 g or more according to a uniform protocol that is unlikely to be duplicated in contemporary studies. The distribution of bilirubin levels was consistent with that reported in the literature (18). Moreover, the exposure of hyperbilirubinemia in this study was not confounded by phototherapy, making the CPP particularly suitable to study the association between untreated neonatal jaundice and childhood asthma.

Our study also has limitations. First, asthma was defined in the 1960s as “a disease of the respiratory passages characterized by dyspnea of an obstructive type which is predominantly expiratory, reversible at least partially, and of varying severity and duration” (31). The immunoglobulin E test, the skin test for allergens, and spirometry had been recently introduced to clinical use at that time. In the absence of laboratory test results, asthma may be underdiagnosed when children have persistent nocturnal coughs but no wheezing or breathlessness and coughing after exercise (32, 33). However, even today it is difficult to monitor lung function in children younger than 7 years (34). In practice, the diagnosis of asthma in young children is often made largely on the basis of symptom patterns and a careful clinical assessment of family history and physical findings, which is not very different from the method used 50 years ago (35).

On the other hand, misclassification of asthma may not be a serious issue in our study because we included only

“definite asthma” confirmed by pediatricians and neurologists and excluded suspected asthma. Moreover, although asthma diagnosis has changed with time, the misclassification of asthma may not necessarily differ in high- and low-bilirubin groups. This nondifferential misclassification in terms of bilirubin level may bias the results toward the null (i.e., underestimating the true effect size). In our data, the prevalence of asthma was associated with maternal allergic diseases. The trend of asthma was similar to that reported in the literature when stratified by other characteristics, such as marital status, number of previous deliveries, and breastfeeding (16). All of the above patterns indicate that the diagnosis of asthma in the CPP may still be acceptable even according to contemporary criteria.

However, cesarean delivery and maternal smoking had no relationship with asthma in this study, which was inconsistent with results of previous studies. This may be attributable to the fact that preterm births and low-birthweight infants were excluded in our study. Because these outcomes are significantly related to smoking during pregnancy, the exclusion of disproportionately more smokers may undermine the association between smoking and asthma. Furthermore, in the 1960s, the cesarean delivery rate was very low (<5%), and babies born via cesarean delivery were likely to have serious health problems. Child deaths and losses to follow-up may also have led to a lower prevalence of asthma among cesarean deliveries and smokers than reported in other studies (16).

In this study, data on gestational age were based on the last menstrual period, which is subject to error. Some term births might actually be preterm (36), causing a false association between hyperbilirubinemia and asthma. However, we found that the magnitude of the association was consistent with that in previous studies, in which gestational age data were more accurate (8). Thus, error in gestational age is an unlikely explanation for our positive finding.

Given that both asthma and neonatal jaundice are common conditions, more studies are warranted to confirm our finding. Comprehension of the underlying biological mechanisms of this association may shed light on the etiology and pathogenesis of asthma. However, it remains possible that both jaundice and asthma are associated with an unmeasured confounder, rendering this association noncausal.

ACKNOWLEDGMENTS

Author affiliation: MOE-Shanghai Key Laboratory of Children’s Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Lisu Huang, Xiaoping Lei, Jun Zhang); Department of Pediatrics, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (Lisu Huang, Yixiao Bao, Yan Chen, Yongjun Zhang); and Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, North Carolina (Zongli Xu).

Lisu Huang and Yixiao Bao contributed equally to the work and should both be considered as first author.

This work was supported by the Natural Science Foundation of China (grant 81273091/H2605).

We thank Dr. Allen J Wilcox and the staff of the Epidemiology Branch at the National Institute of Environmental Health Sciences for their valuable advice.

Conflict of interest: none declared.

REFERENCES

- Vollmer WM, Osborne ML, Buist AS. 20-year trends in the prevalence of asthma and chronic airflow obstruction in an HMO. *Am J Respir Crit Care Med*. 1998;157(4 Pt 1):1079–1084.
- Eder W, Ege MJ, Von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355(21):2226–2235.
- Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. *Pediatrics*. 2011;127(6):1125–1138.
- Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics*. 2012;129(4):735–744.
- Bernsen RM, van der Wouden JC, Nagelkerke NJ, et al. Early life circumstances and atopic disorders in childhood. *Clin Exp Allergy*. 2006;36(7):858–865.
- Cohen SM. Jaundice in the full-term newborn. *Pediatr Nurs*. 2006;32(3):202–208.
- Punnoose AR, Schwartz LA, Golub RM. JAMA patient page. Neonatal hyperbilirubinemia. *JAMA*. 2012;307(19):2115.
- Aspberg S, Dahlquist G, Kahan T, et al. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. *Pediatr Allergy Immunol*. 2010;21(4 Pt 2):e733–e739.
- Ku MS, Sun HL, Sheu JN, et al. Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study. *Pediatr Allergy Immunol*. 2012;23(7):623–628.
- Dobbs RH, Cremer RJ. Phototherapy. *Arch Dis Child*. 1975;50(11):833–836.
- Hardy JB. The Collaborative Perinatal Project: lessons and legacy. *Ann Epidemiol*. 2003;13(5):303–311.
- Von Mutius E. Paediatric origins of adult lung disease. *Thorax*. 2001;56(2):153–157.
- Newman TB, Klebanoff MA. Neonatal hyperbilirubinemia and long-term outcome: another look at the Collaborative Perinatal Project. *Pediatrics*. 1993;92(5):651–657.
- Klebanoff MA. The Collaborative Perinatal Project: a 50-year retrospective. *Paediatr Perinat Epidemiol*. 2009;23(1):2–8.
- Chen TC, Leviton A. Asthma and eczema in children born to women with migraine. *Arch Neurol*. 1990;47(11):1227–1230.
- Metasälä J, Kilkkinen A, Kaila M, et al. Perinatal factors and the risk of asthma in childhood—a population-based register study in Finland. *Am J Epidemiol*. 2008;168(2):170–178.
- Hothorn LA, Vaeth M, Hothorn T. Trend tests for the evaluation of exposure-response relationships in epidemiological exposure studies. *Epidemiol Perspect Innov*. 2009;6:1.
- Alkalay AL, Simmons CF. Hyperbilirubinemia guidelines in newborn infants. *Pediatrics*. 2005;115(3):824–825.
- Aspberg S, Dahlquist G, Kahan T, et al. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? *Pediatr Allergy Immunol*. 2007;18(4):313–319.
- Piazza AJ, Stoll BJ. Jaundice and hyperbilirubinemia in the newborn. In: Kliegman RM, Behrman RE, Jenson HB, et al., eds. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, PA: WB Saunders; 2007:756–766.
- Sarici SU, Serdar MA, Korkmaz A, et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. *Pediatrics*. 2004;113(4):775–780.
- Lu FL, Hsieh CJ, Caffrey JL, et al. Body mass index may modify asthma prevalence among low-birth-weight children. *Am J Epidemiol*. 2012;176(1):32–42.
- Kalliomaki M, Isolauri E. Role of intestinal flora in the development of allergy. *Curr Opin Allergy Clin Immunol*. 2003;3(1):15–20.
- Prachukthum S, Nunnarumit P, Pienvichit P, et al. Genetic polymorphisms in Thai neonates with hyperbilirubinemia. *Acta Paediatr*. 2009;98(7):1106–1110.
- Abdel Ghany EA, Hussain NF, Botros SK. Glutathione S-transferase gene polymorphisms in neonatal hyperbilirubinemia. *J Invest Med*. 2012;60(1):18–22.
- Karam RA, Pasha HF, El-Shal AS, et al. Impact of glutathione-S-transferase gene polymorphisms on enzyme activity, lung function and bronchial asthma susceptibility in Egyptian children. *Gene*. 2012;497(2):314–319.
- Tamer L, Calikoglu M, Ates NA, et al. Glutathione-S-transferase gene polymorphisms (GSTT1, GSTM1, GSTP1) as increased risk factors for asthma. *Respirology*. 2004;9(4):493–498.
- Minelli C, Granell R, Newson R, et al. Glutathione-S-transferase genes and asthma phenotypes: a Human Genome Epidemiology (HuGE) systematic review and meta-analysis including unpublished data. *Int J Epidemiol*. 2010;39(2):539–562.
- Chung EK, Miller RL, Wilson MT, et al. Antenatal risk factors, cytokines and the development of atopic disease in early childhood. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(1):F68–F73.
- Liu Y, Li P, Lu J, et al. Bilirubin possesses powerful immunomodulatory activity and suppresses experimental autoimmune encephalomyelitis. *J Immunol*. 2008;181(3):1887–1897.
- Meneely GR, Renzetti AD Jr, Steele JD, et al. Chronic bronchitis, asthma, and pulmonary emphysema: a statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases. *Am Rev Respir Dis*. 1962;85:762–768.
- Williams H, McNicol KN. Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J*. 1969;4(5679):321–325.
- Speight AN. Is childhood asthma being underdiagnosed and undertreated? *Br Med J*. 1978;2(6133):331–332.
- Lemanske RF, Busse WW. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S95–S102.
- Pedersen SE, Hurd SS, Lemanske RF, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol*. 2011;46(1):1–17.
- Dietz PM, England LJ, Callaghan WM, et al. A comparison of LMP-based and ultrasound-based estimates of gestational age using linked California livebirth and prenatal screening records. *Paediatr Perinat Epidemiol*. 2007;21(suppl 2):62–71.

Web Table 1. The Association between Asthma and Maximum Total Serum Bilirubin Levels in Collaborated Perinatal Project, 1959-1965.

Variable	OR ^a	95% CI
Maximum TSB (mg/dL)		
TSB ≤ 3	ref	ref
3 < TSB ≤ 6	1.08	0.93, 1.27
6 < TSB ≤ 9	1.22	1.04, 1.42
9 < TSB ≤ 15	1.19	0.91, 1.46
TSB > 15	1.61	1.04, 2.08
Gender		
Male	1.76	1.58, 1.96
Female	ref	ref
Race		
White	ref	ref
Black	1.33	1.12, 1.57
Other race	1.30	0.96, 1.76
Gestational age (week)		
37	1.17	0.93, 1.47
38	1.19	0.99, 1.43
39	1.12	0.96, 1.32
40	ref	ref
41	1.16	0.98, 1.39
42	1.09	0.90, 1.33
43	1.13	0.87, 1.47
44	1.08	0.76, 1.54
Study center		
1	ref	ref
2	0.87	0.67, 1.13
3	1.21	0.92, 1.59
4	1.73	1.33, 2.26
5	1.46	1.17, 1.83
6	0.71	0.54, 0.94
7	0.59	0.45, 0.79
8	1.47	1.04, 2.09
9	0.81	0.63, 1.05
10	0.76	0.61, 0.94
11	0.80	0.64, 1.01
12	0.75	0.57, 1.00

a: Generalized Estimating Equation (GEE) Model adjusting for maternal race, gender, gestational age and study center with family number as repeated subject.

TSB, Total serum bilirubin; OR, Odds ratio; CI: Confidence Interval.

Web Table 2. The Association between Asthma and Total Serum Bilirubin Levels at 48-hour Postpartum in Collaborated Perinatal Project, 1959-1965.

Variable	OR ^a	95% CI
TSB at 48-hour (mg/dL)		
TSB ≤ 3	ref	ref
3 < TSB ≤ 6	1.07	0.92, 1.26
6 < TSB ≤ 9	1.23	1.05, 1.44
9 < TSB ≤ 15	1.17	1.02, 1.33
TSB > 15	1.59	0.89, 2.30
Gender		
Male	1.76	1.58, 1.96
Female	ref	ref
Race		
White	ref	ref
Black	1.33	1.12, 1.57
Other race	1.30	0.96, 1.76
Gestational age (week)		
37	1.17	0.93, 1.47
38	1.19	0.99, 1.43
39	1.12	0.96, 1.32
40	ref	ref
41	1.16	0.98, 1.39
42	1.09	0.90, 1.33
43	1.13	0.87, 1.47
44	1.08	0.76, 1.54
Study center		
1	ref	ref
2	0.87	0.67, 1.13
3	1.21	0.92, 1.59
4	1.73	1.33, 2.26
5	1.46	1.17, 1.83
6	0.71	0.54, 0.94
7	0.59	0.45, 0.79
8	1.47	1.04, 2.09
9	0.81	0.63, 1.05
10	0.76	0.61, 0.94
11	0.80	0.64, 1.01
12	0.75	0.57, 1.00

a: Generalized Estimating Equation (GEE) Model adjusting for maternal race, gender, gestational age and study center with family number as repeated subject.

TSB, Total serum bilirubin; OR, Odds ratio; CI: Confidence Interval.