

# Risk Factors for Isolated Biliary Atresia, National Birth Defects Prevention Study, 1997–2002

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Biliary atresia is a rare birth defect that affects 1 in 12,000 to 1 in 19,500 live births. We used data from the National Birth Defects Prevention Study, a multistate case-control study, to identify potential risk factors for isolated biliary atresia (no additional unrelated major birth defects diagnosed). Infants were identified from eight states from 1997 to 2002, with clinical information abstracted from medical records. Potential risk factors assessed include: demographic factors, seasonality, preterm birth, maternal smoking, maternal alcohol use, maternal illicit drug use, maternal health, maternal medication use, maternal vitamin use, and maternal nutrition. Infants of non-Hispanic black mothers were more likely to have biliary atresia than infants of non-Hispanic white mothers (adjusted odds ratio (aOR) = 2.29, 95% confidence interval (CI) 1.07–4.93) and infants conceived during the spring season were more likely to have biliary atresia than infants conceived in winter (aOR = 2.33, 95%CI

1.05–5.16). Low intakes of vitamin E, copper, phosphorus, and beta tocopherol were associated with the occurrence of isolated biliary atresia (borderline significance). Low iron intake had a borderline inverse association with biliary atresia. While this analysis provides support for previous reports of a possible association between seasonal variation and the occurrence of biliary atresia, more data are needed to evaluate whether the seasonal variation is related to infectious agents. The role of nutrients in the development of biliary atresia remains unclear. Further studies of genetic, infectious, and nutrient exposures and the association of biliary atresia are warranted. Published 2007 Wiley-Liss, Inc.†

**Key words:** biliary atresia; epidemiology; risk factors; seasons; infection; nutrition

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## INTRODUCTION

Biliary atresia is a rare birth defect with an estimated prevalence from 1 in 12,000 to 1 in 19,500 live births [Yoon et al., 1997; Chardot et al., 1999; Caton et al., 2004]. It is characterized by inflammation and obliteration of the extrahepatic and intrahepatic bile ducts resulting in fulminant hepatic failure and death at any early age without appropriate surgical intervention, with liver transplantation required for most cases [Balistreri et al., 1996; Narkewicz, 2001; Perlmutter and Shepherd, 2002; Schreiber and Kleinman, 2002; Sokol et al., 2003; Hinds et al., 2004; Mack and Sokol, 2005]. Two recognized forms of biliary atresia have

been described: the embryonic form and the perinatal form [Balistreri et al., 1996; Narkewicz, 2001; Perlmutter and Shepherd, 2002; Schreiber and Kleinman, 2002; Sokol et al., 2003; Hinds et al., 2004]. The embryonic form is associated with at least one other major congenital anomaly, and

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frequently biliary atresia is part of a complex group of congenital anomalies that result from situs abnormalities. Infants with the embryonic form of the birth defect have an early onset of jaundice and cholestasis; the perinatal form of biliary atresia is characterized by a later onset of jaundice and cholestasis, bile duct remnants, and no other congenital anomalies. Approximately 67–91% of all infants with biliary atresia occur as isolated cases, and are presumed to be the perinatal form of the disease [Yoon et al., 1997; Chardot et al., 1999; Caton et al., 2004]. The etiology of biliary atresia is believed to be multifactorial and involve factors that disrupt normal development of the biliary tree, or inflame and obstruct portals during the prenatal period until 3 months of age [Balistreri et al., 1996; Narkewicz, 2001; Perlmutter and Shepherd, 2002; Schreiber and Kleinman, 2002; Sokol et al., 2003; Hinds et al., 2004; Mack and Sokol, 2005]. Although both genetic and environmental risk factors undoubtedly play a role in the different forms of biliary atresia, the perinatal form is thought to be more likely caused by infectious, toxic, vascular, or immune agents [Sokol et al., 2003; Hinds et al., 2004; Mack and Sokol, 2005].

Because biliary atresia is rare, few potential risk factors have been identified. Previous epidemiologic studies have suggested maternal age, gravidity and parity, gestational age, infant sex, small for gestational age (intrauterine growth retardation), season and month of birth, birth weight, region of birth, and race or ethnicity as potential risk factors for biliary atresia [Shim et al., 1974; Danks et al., 1977; Strickland and Shannon, 1982; Houwen et al., 1988; Vic et al., 1994; Ayas et al., 1996; Yoon et al., 1997; Chardot et al., 1999; Fischler et al., 2002; Caton et al., 2004]. The notable seasonal variation of biliary atresia raises the possibility of a link to certain infectious pathogens that follow a seasonal pattern. Additionally, nutrient deficiencies during gestation have been shown to be associated with immune deficiency and susceptibility to infection in children; therefore, certain nutrients may be involved in the development of biliary atresia [Cunningham-Rundles et al., 2005]. Alternatively, nutritional deficiencies might have a more direct role on the development of biliary atresia. Because the association of biliary atresia with these potential risk factors remains unclear, we used data from the National Birth Defects Prevention Study (NBDPS) to assess potential risk factors this condition.

## METHODS

### Data Sources and Population

We used data from the NBDPS, a multistate case-control study designed to investigate genetic and environmental risk factors of major birth defects. A detailed description of the NBDPS methods has

been published elsewhere [Yoon et al., 2001]. Briefly, case infants are identified through ongoing population-based birth defects surveillance systems in eight states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas), with six of these sites including information on prenatally diagnosed case infants. Case infants with a known etiology such as chromosomal abnormalities and single-gene conditions are excluded from the study. Control infants for the NBDPS are infants with no major birth defects randomly selected from the same source population as the case infants through birth certificates or birth hospitals. Maternal interviews are conducted via telephone in English or Spanish using a standardized questionnaire, and are completed no earlier than 6 weeks after the infant's estimated date of delivery (EDD) and no later than 24 months after EDD.

### Case Classification

A clinical geneticist at each site reviews case information from hospital reports and medical records to ensure that each case meets the standard case definition. For this investigation, case infants were defined as infants with biliary atresia (NBDPS codes 751650—Biliary atresia, extrahepatic or not otherwise specified). Each case was re-reviewed by a clinical geneticist (C. Moore) and classified as: (1) isolated—infants with biliary atresia as a solitary anomaly, with additional minor anomalies or with additional major anomalies that are related to biliary atresia (sequence); (2) multiple—infants with biliary atresia and at least one additional major unrelated congenital anomaly; or (3) complex—infants with biliary atresia in association with a situs anomaly [Rasmussen et al., 2003]. Case infants classified as multiple or complex were excluded from further analysis of potential risk factors because these cases are unlikely to have the same causal factors as isolated cases [Sokol et al., 2003; Hinds et al., 2004; Mack and Sokol, 2005]. Case and control infants for this analysis were limited to births on or after October 1, 1997, and infants with an EDD on or before December 31, 2002, with a complete maternal interview.

### Exposure Classification

The NBDPS collects information on demographic factors and a wide assortment of environmental exposures including smoking history, alcohol use, illicit drug use, maternal health and medication use, vitamin use, and nutrition. Detailed questions concerning maternal infection are included in the maternal health section. Mothers were asked about respiratory infections, genitourinary infections, and other infectious diseases from 3 months before pregnancy until the end of pregnancy. For this analysis, a clinician reviewed the reported illnesses

blinded to case-control status and determined which illnesses were of an infectious nature. Additionally, mothers were asked to report any fever (which might have been a non-specific reflection of underlying infection) and use of selected medications during the same time period. We grouped reported medications for the following three categories: anti-infectives, antipyretics, and antitussive/expectorants. These three medication groups were selected because their use might indicate the presence of a maternal infection. Mothers reported start and stop dates for each illness, fever, and medication. Because the timing of the malformation is not clear and might occur at any time prenatally to 3 months of age, the exposure periods analyzed were: periconceptional period (1 month before pregnancy to the third month of pregnancy), second trimester, and third trimester.

Given the strong association between biliary atresia and preterm birth, we examined seasonality of biliary atresia through month and season of conception. The estimated date of conception was calculated for each case and control infants by subtracting 38 weeks from the reported EDD. Additionally, month and season of birth were examined in order to facilitate comparisons with earlier research. Months of conception and birth were collapsed into four seasons: spring (March–May), summer (June–August), autumn (September–November), and winter (December–February).

Maternal smoking during pregnancy was ascertained through the maternal interview. Environmental tobacco smoke (second-hand smoke) exposure was defined as self reported exposure to tobacco smoke at home or work among mothers who reported no active smoking during pregnancy.

An abbreviated Willett Food Frequency Questionnaire was used to assess the frequency of intake for 58 food items for the year prior to pregnancy [Willett et al., 1987]. During the telephone interview, the average frequency of intake of the food item was ascertained with each food item having a standard serving size on which the question was based. Nutrient values were calculated using this frequency and the United States Department of Agriculture National Standard Reference 16-1. All nutrient values were adjusted for energy using the nutrient density approach (quantity per 1,000 kcal) and categorized into quartiles. Quartiles were derived from intake distributions among the control mothers. Since few nutrients in the quartile analysis were associated with biliary atresia, we dichotomized nutrients with a moderate association ( $P < 0.50$ ) to improve power, by combining categories with the most homogenous effect estimates. After examining crude odds ratios (ORs) across the quartiles, we collapsed groups in which the ORs were similar and created dichotomous variables that resulted in the highest quartile, highest two quartiles, or highest three quartiles as the referent groups.

Demographic factors and other variables examined in this study included: maternal age (<25 years, 25–34 years, or >34 years); maternal race or ethnicity (non-Hispanic White, non-Hispanic Black, or Other); maternal body mass index (normal/underweight or overweight/obese); education (less than high school, high school graduate, or more than high school); gravidity (primigravid or multigravid); parity ( $\leq 1$  or  $> 1$ ); study site (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, or Georgia); annual household income (<\$20,000 or  $\geq$ \$20,000); periconceptional maternal folic acid-containing supplement use (yes or no); periconceptional maternal smoking (yes or no); periconceptional maternal alcohol use (yes or no); infant gender (female or male); preterm birth ( $\leq 36$  weeks or  $> 36$  weeks gestation); birthweight (<2,500 or  $\geq 2,500$  g); and plurality (singleton or multiple births).

### Analytic Methods

Initially, we examined the proportion of infants with biliary atresia by case classification (isolated, multiple, or complex). For non-dietary variables, crude ORs were calculated for the association between potential risk factors and the occurrence of isolated biliary atresia using stratified analyses. We then used logistic regression to assess whether risk factors that were significantly associated at the crude level remained associated with biliary atresia while controlling for potential confounders. The potential confounders were evaluated by a change-in-estimate criterion of 10%. Covariates that met this criterion were used to obtain an adjusted model.

For dietary variables, crude ORs were also calculated using stratified analyses. We selected three nutrients (folate, cholesterol, and fiber) and developed three separate models using a change-in-estimate criterion of 10%. We selected these three nutrients because they represent a wide range of nutrients within the database (macronutrients, micronutrients, and non-nutrient). Any variables found to be confounders of the association between any of these three nutrients and biliary atresia were included in the final model for all nutrients. Nutrients in the final model were adjusted for maternal body mass index, annual household income, maternal race or ethnicity, and maternal age.

Descriptive and statistical analyses were conducted using SAS software program 9.1 (SAS Institute, Cary, NC).

### RESULTS

For the period from 1997 to 2002, 112 cases of biliary atresia were identified and 71% of these mothers participated in the NBDPS interview. Maternal interviews were completed for 79 case

TABLE I. Clinical Characteristics of Biliary Atresia in the National Birth Defects Prevention Study, 1997–2002

Characteristic	Isolated defect <sup>a</sup> (n = 62)	Multiple major defects (n = 11)	Situs anomaly (n = 6)
Sex			
Female	32 (51.61%)	4 (36.36%)	6 (100%)
Male	30 (48.39%)	7 (63.64%)	0 (0%)
Gestational age (weeks)			
Preterm ( $\leq 36$ )	10 (16.13%)	5 (45.45%)	1 (16.67%)
Term ( $\geq 37$ )	52 (83.87%)	6 (54.55%)	5 (83.33%)
Birth weight (g)			
Low birthweight (<2,500)	5 (8.06%)	5 (45.45%)	1 (16.67%)
Normal birthweight ( $\geq 2,500$ )	57 (91.94)	6 (54.55%)	5 (83.33%)
Plurality			
Singleton	59 (95.16%)	11 (100%)	6 (100%)
Multiple	3 (4.84%)	0 (0%)	0 (0%)
Birth outcome			
Live birth	62 (100%)	11 (100%)	6 (100%)
Fetal death	0 (0%)	0 (0%)	0 (0%)
<20 weeks			
Fetal death	0 (0%)	0 (0%)	0 (0%)
$\geq 20$ weeks			
Induced abortion	0 (0%)	0 (0%)	0 (0%)
Maternal age (years)			
<25	25 (40.32%)	7 (63.64%)	2 (33.33%)
25–34	31 (50.00%)	3 (27.27%)	2 (33.33%)
$\geq 35$	6 (9.68%)	1 (9.09%)	2 (33.33%)
Maternal race or ethnicity <sup>b</sup>			
White, not Hispanic	28 (45.16%)	6 (54.55%)	3 (50.00%)
Black, not Hispanic	14 (22.58%)	3 (27.27%)	1 (16.67%)
Hispanic	17 (27.42%)	1 (9.09%)	2 (33.33%)
Other	3 (4.84%)	1 (9.09%)	0 (0%)

<sup>a</sup>Only case infants with isolated biliary atresia are included in subsequent tables and analyses.

<sup>b</sup>Maternal race or ethnicity is taken from the medical records for this table. Mothers with more than one reported race/ethnicity are classified as "Other".

infants with biliary atresia and 4,094 control infants in the NBDPS. Among the 79 case infants, 62 (78%) were classified as isolated, 11 (14%) as multiple, and 6 (8%) as complex (Table I). The 11 case infants classified as multiple and the 6 case infants classified as complex were excluded from further analysis, which resulted in a sample of 62 infants with isolated biliary atresia (cases) for the analyses.

Maternal age, maternal education, maternal smoking or alcohol use during the periconceptional period, maternal folic acid use during the periconceptional period, gravidity, parity, study site, family income, infant sex, preterm birth, infant birthweight, and plurality were not associated with the occurrence of biliary atresia (Table II). Unadjusted analyses revealed that infants of non-Hispanic Black mothers were 2.50 times more likely to have isolated biliary atresia than infants of non-Hispanic White mothers. Infants conceived during the spring were more likely to have biliary atresia than infants conceived during the winter months (OR = 2.18, 95% confidence interval (CI): 1.02–4.65). In contrast, self-reported infection was inversely associated with biliary atresia (OR = 0.41, 95%CI: 0.22–0.78)

as was self-reported respiratory infection (OR = 0.46, 95%CI: 0.22–0.94) during the periconceptional period. However, respiratory infections during the second or third trimester were not associated with biliary atresia. Similarly, gastrointestinal infections, genitourinary infections, maternal fevers, and maternal medication use during any trimester of pregnancy were not associated with biliary atresia. After controlling for confounding, season of conception, periconceptional maternal infection, and maternal race remained significantly associated with biliary atresia (Table III).

In the unadjusted analyses of reported nutrient intake, case mothers were more likely to have lower intakes of vitamin E, potassium, copper, calcium, magnesium, phosphorus, pantothenic acid, and beta tocopherol than control mothers. After adjusting for maternal age, maternal BMI, maternal race or ethnicity, and annual household income, none of the nutrients remained significantly associated with the occurrence of isolated biliary atresia (Table IV). However, several nutrients had adjusted effects with borderline significance including low intakes of vitamin E (adjusted odds ratio (aOR) = 2.02, 95%CI: 0.95–4.31), copper (aOR = 1.62, 95%CI: 0.93–2.83),

TABLE II. Maternal and Infant Characteristics for Isolated Cases of Biliary Atresia and Infants With No Major Birth Defects (Controls), National Birth Defects Prevention Study, 1997–2002

Characteristic	Cases (n = 62)	%	Controls (n = 4,094)	%	Crude odds ratio (OR)	95% Confidence interval (CI)
Maternal age (years)						
<25	25	40.32	1,339	32.71	1.31	0.77–2.22
25–34	31	50.00	2,170	53.00	1.00	—
>35	6	9.68	585	14.29	0.72	0.30–1.73
Maternal race						
White, non-Hispanic	28	45.16	2,456	60.15	1.00	—
Black, non-Hispanic	14	22.58	491	12.03	2.50	1.31–4.79
Hispanic	17	27.42	931	22.80	1.60	0.87–2.94
Other	3	4.84	205	5.02	1.28	0.25–4.21 <sup>a</sup>
Maternal education						
<12 years	12	19.35	676	16.54	1.24	0.64–2.41
12 years	16	25.81	1,030	25.21	1.09	0.60–1.98
>12 years	34	54.84	2,380	58.25	1.00	—
Gravidity						
Primigravid	18	29.03	1,171	28.62	1.00	—
Multigravid	44	70.97	2,921	71.38	0.98	0.56–1.70
Parity						
≤1	48	77.42	3,080	75.27	1.00	—
>1	14	22.58	1,012	24.73	0.89	0.49–1.62
Body mass index						
Underweight/normal	35	58.33	2,487	63.23	1.00	—
Obese/overweight	25	41.67	1,446	36.77	1.23	0.73–2.06
Study site						
Arkansas	6	9.68	499	12.19	0.55	0.20–1.53
California	12	19.35	597	14.58	0.92	0.39–2.15
Iowa	5	8.06	479	11.70	0.48	0.16–1.41
Massachusetts	9	14.52	535	13.07	0.77	0.31–1.91
New Jersey	4	6.45	575	14.04	0.32	0.07–1.11 <sup>a</sup>
New York	6	9.68	448	10.94	0.61	0.22–1.70
Texas	10	16.13	503	12.29	0.91	0.38–2.21
CDC/Atlanta	10	16.13	458	11.19	1.00	—
Family income (annual)						
<\$20,000	21	35.59	1,115	31.27	1.21	0.71–2.08
≥\$20,000	38	64.41	2,451	68.73	1.00	—
Periconceptional <sup>b</sup> use of folic acid-containing supplements						
No use	10	16.13	581	14.19	1.16	0.59–2.30
Any use	52	83.87	3,513	85.81	1.00	—
Periconceptional <sup>b</sup> maternal smoking						
Smoker	9	14.52	798	19.49	0.69	0.33–1.42
Non-Smoker, exposed to ETS <sup>c</sup>	10	16.13	657	16.05	0.93	0.47–1.86
Non-Smoker, unexposed to ETS <sup>c</sup>	43	69.35	2,630	64.24	1.00	—
Periconceptional <sup>b</sup> maternal alcohol use						
Yes	25	40.32	1,591	39.02	1.06	0.63–1.76
No	37	59.68	2,486	60.98	1.00	—
Infant sex						
Female	32	51.61	2,040	49.89	1.07	0.65–1.77
Male	30	48.39	2,049	50.11	1.00	—
Gestational age (weeks)						
Preterm (≤36)	10	16.13	365	8.92	1.96	0.99–3.90
Term (>36)	52	83.87	3,726	91.01	1.00	—
Birth weight						
Low birthweight (LBW)	5	8.06	237	5.79	1.42	0.56–3.58
Normal birthweight (NBW)	57	91.94	3,836	93.70	1.00	—
Weight for gestational age						
Preterm, LBW	3	4.84	174	4.28	1.26	0.25–3.95 <sup>a</sup>
Term, LBW	2	3.23	63	1.55	2.32	0.27–9.16 <sup>a</sup>
Preterm, NBW	7	11.29	186	4.57	2.75	1.23–6.14

(Continued)

TABLE II. (Continued)

Characteristic	Cases (n = 62)	%	Controls (n = 4,094)	%	Crude odds ratio (OR)	95% Confidence interval (CI)
Term, NBW	50	80.65	3,647	89.61	1.00	—
Plurality						
Singleton	59	95.16	3,959	96.82	1.00	—
Multiple births	3	4.84	130	3.18	1.55	0.31–4.85 <sup>a</sup>
Periconceptual <sup>b</sup> maternal gastrointestinal infection						
Yes	1	1.61	15	0.37	—	—
No	61	98.39	4,070	99.63	—	—
Second trimester maternal gastrointestinal infection						
Yes	1	1.61	12	0.29	—	—
No	61	98.39	4,073	99.71	—	—
Third trimester maternal gastrointestinal infection						
Yes	1	1.61	4	0.10	—	—
No	61	98.39	4,081	99.90	—	—
Periconceptual <sup>b</sup> maternal genitourinary infection						
Yes	3	4.92	458	11.33	0.41	0.08–1.25 <sup>a</sup>
No	58	95.08	3,586	88.67	1.00	—
Second trimester maternal genitourinary infection						
Yes	8	13.33	462	11.43	1.19	0.56–2.52
No	52	86.67	3,579	88.57	1.00	—
Third trimester maternal genitourinary infection						
Yes	5	8.80	473	11.70	0.67	0.27–1.69
No	56	91.80	3,571	88.30	1.00	—
Periconceptual <sup>b</sup> maternal respiratory infection						
Yes	9	16.07	1,163	29.41	0.46	0.22–0.94
No	47	83.93	2,792	70.59	1.00	—
Second trimester maternal respiratory infection						
Yes	9	16.07	937	23.69	0.62	0.30–1.26
No	47	83.93	3,018	76.31	1.00	—
Third trimester maternal respiratory infection						
Yes	10	17.89	665	16.81	1.08	0.54–2.14
No	46	82.14	3,290	83.19	1.00	—
Periconceptual <sup>b</sup> maternal infection (any infection)						
Yes	12	19.35	1,503	36.83	0.41	0.22–0.78
No	50	80.65	2,578	63.17	1.00	—
Second trimester maternal infection (any infection)						
Yes	16	26.23	1,297	31.80	0.76	0.43–1.35
No	45	73.77	2,782	68.20	1.00	—
Third trimester maternal infection (any infection)						
Yes	16	25.81	1,054	25.88	1.00	0.56–1.77
No	46	74.19	3,019	74.12	1.00	—
Periconceptual <sup>b</sup> maternal fever						
Yes	5	8.06	487	11.90	0.65	0.26–1.63
No	57	91.94	3,606	88.10	1.00	—
Second trimester maternal fever						
Yes	4	6.45	377	9.21	0.68	0.18–1.85 <sup>a</sup>
No	58	93.55	3,716	90.79	1.00	—
Third trimester maternal fever						
Yes	5	8.06	299	7.31	1.11	0.44–2.80
No	57	91.94	3,794	92.69	1.00	—
Periconceptual <sup>b</sup> maternal use of antipyretics						
Yes	40	64.52	2,656	64.88	0.98	0.58–1.66
No	22	35.48	1,438	35.12	1.00	—
Second trimester maternal use of antipyretics						
Yes	36	58.06	2,215	54.10	1.17	0.71–1.95
No	26	41.94	1,879	45.90	1.00	—
Third trimester maternal use of antipyretics						
Yes	34	54.84	2,124	51.88	1.13	0.68–1.86
No	28	45.16	1,970	48.12	1.00	—
Periconceptual <sup>b</sup> maternal use of antiinfectives						
Yes	4	6.45	612	14.95	0.39	0.10–1.07 <sup>a</sup>
No	58	93.55	3,482	85.05	1.00	—
Second trimester maternal use of antiinfectives						
Yes	8	12.90	581	14.19	0.90	0.42–1.89
No	54	87.10	3,513	85.81	1.00	—

TABLE II. (Continued)

Characteristic	Cases (n = 62)	%	Controls (n = 4,094)	%	Crude odds ratio (OR)	95% Confidence interval (CI)
Third trimester maternal use of antiinfectives						
Yes	6	9.68	491	11.99	0.79	0.34–1.83
No	56	90.32	3,603	88.01	1.00	—
Periconceptional <sup>b</sup> maternal use of antitussives or expectorants						
Yes	1	1.61	346	8.45	—	—
No	61	98.39	3,748	91.55	—	—
Second trimester maternal use of antitussives or expectorants						
Yes	3	4.84	274	6.69	0.71	0.14–2.20
No	59	95.16	3,820	93.31	—	—
Third trimester maternal use of antitussives or expectorants						
Yes	2	3.23	226	5.52	0.57	0.07–2.18
No	60	96.77	3,868	94.48	1.00	—
Season of conception <sup>d</sup>						
Spring	21	33.87	996	24.33	2.18	1.02–4.65
Summer	11	17.74	975	23.82	1.17	0.49–2.76
Autumn	20	32.26	1,090	26.62	1.90	0.88–4.07
Winter	10	16.13	1,033	25.23	1.00	—
Season of birth <sup>d</sup>						
Spring	7	11.29	986	24.08	0.33	0.14–0.79
Summer	23	37.10	1,087	26.55	0.99	0.55–1.80
Autumn	11	17.74	1,036	25.31	0.50	0.24–1.04
Winter	21	33.87	985	24.01	1.00	—

Missing data not shown.

<sup>a</sup>Exact confidence limits computed.

<sup>b</sup>Periconceptional period is 1 month prior to pregnancy until end of the first trimester.

<sup>c</sup>ETS—environmental tobacco smoke.

<sup>d</sup>Spring, March–May; Summer, June–August; Autumn, September–November; Winter, December–February.

phosphorus (aOR = 1.60, 95%CI: 0.91–2.82), and beta tocopherol (aOR = 1.64, 95%CI: 0.92–2.91), and low iron intake had a borderline inverse association with biliary atresia (aOR = 0.47, 95%CI: 0.22–1.01).

## DISCUSSION

The findings of this case-control epidemiologic study of potential risk factors for biliary atresia illustrate that case infants were more likely to have non-Hispanic Black mothers and be born

preterm than control infants. The possible role of an infectious etiology of biliary atresia remains unclear from the results. Mothers of case infants were less likely to report an infection during the periconceptional period than control infants, but season of birth and conception were associated with biliary atresia (borderline significance in adjusted analyses). Several nutrients were also associated with the occurrence of biliary atresia in crude analysis and had borderline significance after controlling for potential confounders.

Several of the factors analyzed in this study were consistent with the previous literature. For example, 78% of the case infants in this study had isolated biliary atresia, which is consistent with previous reports and reviews [Balistreri et al., 1996; Yoon et al., 1997; Chardot et al., 1999; Perlmutter and Shepherd, 2002; Schreiber and Kleinman, 2002; Sokol et al., 2003; Caton et al., 2004; Hinds et al., 2004; Mack and Sokol, 2005]. Also consistent with previous investigations, we found that case infants were more likely to be low birthweight and preterm than control infants [Yoon et al., 1997; Fischler et al., 2002; Caton et al., 2004]. Finally, in accordance with other United States studies examining race and biliary atresia, non-Hispanic Black mothers were more likely to give birth to an infant with biliary atresia than non-Hispanic White mothers even after controlling for income [Yoon et al., 1997; Caton et al., 2004].

Conversely, some important differences were noted when comparing these results to others studies. Some

TABLE III. Adjusted Analyses of Isolated Cases of Biliary Atresia, National Birth Defects Prevention Study, 1997–2002

Characteristic	Adjusted odds ratio	95% Confidence interval
Season of conception <sup>a</sup>		
Spring	2.33	1.05–5.16
Summer	1.38	0.57–3.35
Autumn	2.00	0.90–4.45
Winter	1.00	—
Periconceptional maternal infection <sup>b</sup>		
Yes	0.41	0.22–0.78
No	1.00	—
Race <sup>c</sup>		
Other	1.26	0.60–2.64
Black, non-Hispanic	2.29	1.07–4.93
White, non-Hispanic	1.00	—

<sup>a</sup>Model adjusted for annual household income, site, and gestational age. Model included 59 cases and 3,563 controls.

<sup>b</sup>No confounders. Model included 62 cases and 4,081 controls.

<sup>c</sup>Model adjusted for family income, site, and gestational age. Model included 59 cases and 3,557 controls.

TABLE IV. Unadjusted and Adjusted Associations Between Maternal Nutrients and the Occurrence of Isolated Biliary Atresia, National Birth Defects Prevention Study, 1997–2002

Characteristics	Cases (n = 62)	Controls (n = 4,094)	Crude odds ratio	95% Confidence interval	Adjusted <sup>a</sup> odds ratio	95% Confidence interval
Quartile 1, 2, and 3 (Low) vs. Quartile 4 (High)						
Fiber						
Low (<13.54 g/kcal)	51	3,070	1.55	0.80–2.98	1.40	0.69–2.84
Sodium						
Low (<99.32 mg/kcal)	51	3,069	1.74	0.88–3.43	1.60	0.80–3.22
Vitamin C						
Low (<11.00 mg/kcal)	51	3,070	1.73	0.88–3.42	1.63	0.81–3.26
Riboflavin						
Low (<1.46 mg/kcal)	50	3,070	1.39	0.74–2.62	1.10	0.57–2.10
Niacin						
Low (<13.61 mg/kcal)	48	3,070	1.14	0.63–2.08	1.04	0.57–1.93
Folate, food						
Low (<180.84 µg/kcal)	51	3,070	1.55	0.80–2.98	1.47	0.75–2.89
Vitamin E						
Low (<3.90 mg/kcal)	54	3,069	2.25	1.07–4.75	2.02	0.95–4.31
Cholesterol						
Low (<179.47 mg/kcal)	43	3,070	0.75	0.44–1.30	0.94	0.52–1.67
Quartile 1 and 2 (Low) vs. Quartile 3 and 4 (High)						
Potassium						
Low (<1,735.16 mg/kcal)	40	2,046	1.82	1.08–3.07	1.52	0.87–2.65
Copper						
Low (<0.83 mg/kcal)	39	2,047	1.69	1.01–2.85	1.62	0.93–2.83
Quartile 1 (Low) vs. Quartile 2, 3, and 4 (High)						
Calcium						
Low (<357.76 mg/kcal)	25	1,023	2.03	1.21–3.38	1.48	0.85–2.58
Iron						
Low (<6.05 mg/kcal)	10	1,024	0.58	0.29–1.14	0.47	0.22–1.01
Magnesium						
Low (<132.78 mg/kcal)	23	1,023	1.77	1.05–2.98	1.38	0.77–2.49
Phosphorus						
Low (<637.21 mg/kcal)	25	1,023	2.03	1.21–3.38	1.60	0.91–2.82
Manganese						
Low (<0.99 mg/kcal)	20	1,023	1.43	0.84–2.45	1.25	0.70–2.22
Thiamin						
Low (<0.62 mg/kcal)	19	1,023	1.33	0.77–2.29	1.09	0.60–1.97
Pantothenic acid						
Low (<2.38 mg/kcal)	23	1,024	1.77	1.05–2.97	1.43	0.81–2.52
Vitamin B6						
Low (<1.01 mg/kcal)	14	1,023	0.88	0.48–1.59	0.66	0.34–1.28
Folate, total						
Low (<197.03 µg/kcal)	19	1,023	1.33	0.77–2.29	1.19	0.67–2.13
Beta tocopherol						
Low (<0.02 mg/kcal)	23	1,022	1.77	1.05–2.98	1.64	0.92–2.91
Gamma tocopherol						
Low (<0.39 mg/kcal)	45	3,069	0.88	0.50–1.55	0.80	0.45–1.42

<sup>a</sup>Adjusted for maternal race or ethnicity, maternal body mass index, maternal age, and annual household income.

studies have suggested an increased risk for giving birth to an infant with biliary atresia among older mothers, and some reviews have suggested that there is an overall female predominance of biliary atresia (female/male = 1.2:1) [Balistreri et al., 1996; Lefkowitz, 1998; Narkewicz, 2001; Sokol et al., 2003]. However, our study along with studies in Atlanta and New York state, did not support the findings that maternal age and infant sex were associated with isolated biliary atresia [Yoon et al., 1997; Caton et al., 2004].

Epidemiologic studies investigating seasonal variations of biliary atresia have produced inconsistent results [Shim et al., 1974; Danks et al., 1977;

Strickland and Shannon, 1982; Houwen et al., 1988; Ayas et al., 1996; Yoon et al., 1997; Chardot et al., 1999; Fischler et al., 2002; Caton et al., 2004]. In the current study, infants conceived in the spring or autumn were more likely to have biliary atresia than infants conceived in the winter or summer. Seasonal variation was also observed in Texas, New York, and Atlanta studies [Strickland and Shannon, 1982; Yoon et al., 1997; Caton et al., 2004], but not in studies from Sweden, Hawaii, the Netherlands and West Germany, Michigan, and France [Shim et al., 1974; Danks et al., 1977; Houwen et al., 1988; Chardot et al., 1999; Fischler et al., 2002]. These discrepancies could be attributed to differences in case inclusion criteria

and small sample size. Only three of the studies (France, Atlanta, and New York state) limited their analyses to isolated cases of biliary atresia whereas the other six studies included isolated/sequence, multiple, and syndromic cases of biliary atresia. The Atlanta study identified a weak seasonal pattern among the 49 isolated cases of biliary atresia during a 26-year period [Yoon et al., 1997]. However, the results of this study should be interpreted cautiously given the small sample size. The New York study also observed a significant seasonal pattern from the 249 isolated cases of biliary atresia identified from 1983 to 1998 [Caton et al., 2004]. The prevalence of biliary atresia in New York State (excluding New York City) was nearly three times greater among births in autumn than in summer. While the timing of seasonal variation in the New York study differs from the current study, these differences could occur for several reasons including geographic variation in the seasonal patterns of certain pathogens. The study conducted in France did not find any seasonal variation from the 385 isolated cases of biliary atresia identified from 1986 to 1996 [Chardot et al., 1999]. Using a  $\chi^2$  test and the Walter and Elwood Test for seasonality, no seasonal variation of biliary atresia was identified. While this French study had greater power to detect any seasonal variations, the authors did not control for potential confounders such as race or maternal infection. The discrepancies in findings between the French and United States' studies might be attributed to regional variations in the racial or ethnic groups or variations of particular viruses endemic to the regions.

Previously, seasonal patterns of biliary atresia have been interpreted as evidence for an infectious etiology [Narkewicz, 2001; Sokol et al., 2003; Mack and Sokol, 2005]. To our knowledge, this study is the first epidemiologic study to examine whether reported maternal infection, maternal fever, or medication use were associated with biliary atresia. We found a significant inverse association between reported maternal infection during the periconceptual period and biliary atresia, but no such association was observed for maternal fever or medication use. While infection was more common among controls during the periconceptual period, the severity of the infection was nearly identical for both case and control mothers. The proportion of case and control mothers experiencing fever or using medications during infection was approximately 80%. Therefore, it is not likely that mothers of case infants experienced fewer but more severe infections than mothers of control infants. We were unable to definitively assess whether biliary atresia is associated with an infectious etiology for several reasons. The majority of mothers reporting an infection during pregnancy reported having a respiratory illness; however, the pathogens most often involved in respiratory illness are not those

most likely to be causal factors for biliary atresia [Garcia-Garcia et al., 2006]. Previous studies of biliary atresia have suggested rotavirus [Riepenhoff-Talty et al., 1993, 1996; Petersen et al., 1997; Czech-Schmidt et al., 2001], cytomegalovirus [Tarr et al., 1996; Fischler et al., 1998; Oliveira et al., 2002], and reovirus [Rosenberg et al., 1983; Glaser et al., 1984; Morecki et al., 1984a,b; Tyler et al., 1998] which typically cause gastrointestinal illness [Espejo et al., 1977; Middleton, 1996] might contribute to the development of biliary atresia. However, other studies examining these same viruses cannot consistently replicate these findings [Dussaix et al., 1984; Brown et al., 1988; Chang et al., 1992; Steele et al., 1995; Bobo et al., 1997; Jevon and Dimmick, 1999]. Our study had only one case-mother reporting gastrointestinal illness in the periconceptual period, limiting our capacity to evaluate the impact of gastrointestinal infections.

Our study was the first to examine the association between maternal nutrients and biliary atresia. We examined nutrient intakes for several reasons. Nutrient deficiencies in mothers prior to pregnancy have been shown to be associated with certain birth defects, including neural tube defects and orofacial clefts [Mulinare et al., 1988; Czeizel, 1993; Tolarova and Harris, 1995; Hayes et al., 1996; Berry et al., 1999]. Additionally, nutrient deficiencies during gestation and early infancy have been associated with abnormal immune development and increased risk of infections in children [Cunningham-Rundles et al., 2005]. Specifically, deficiencies in protein, zinc, iron, copper, selenium, vitamin A, vitamin E, and vitamin C intake have been shown to promote certain infectious processes. While not statistically significant in multivariate analyses, our data suggest a possible role of vitamin E, copper, iron, phosphorus, and beta tocopherol in the development of biliary atresia. These results warrant further investigation.

Several methodological limitations in this study need to be considered when interpreting the results. The small number of cases raised several problems, including low power and the inability to examine the effect of numerous risk factors simultaneously as additional stratification created several unstable effect estimates. Another limitation is the retrospective reporting of several exposures. The lack of association between biliary atresia and maternal infection might have been attributed to the retrospective ascertainment of maternal infections. Voldsgaard et al. [2002], found that mothers significantly underreported maternal influenza after giving birth in comparison to reports during the 25th week of pregnancy. In case-control studies, recall bias is of concern and we would have anticipated that case mothers would have been more likely to recall certain exposures than control mothers [Werler et al., 1989]; however, in the NBDPS, case mothers reported maternal infection during

pregnancy less often than control mothers. Therefore, we do not believe the retrospective ascertainment of maternal infection significantly influenced our findings. Lastly, dietary data were assessed using a food frequency questionnaire and were subject to the errors inherent in this mode of data collection [Willett et al., 1987; Willett, 1998]. While previous studies in U.S. populations have observed that self-reported smoking during pregnancy is reasonably reliable and valid, the accuracy of self-reported alcohol use during pregnancy has not been as well demonstrated [Ernhart et al., 1988; Tomeo et al., 1999; Klebanoff et al., 2001; Christensen et al., 2004; Alvik et al., 2005].

In spite of the limitations, there were several important strengths of this analysis. First, our study analyzed data obtained from a population-based case-control study of major birth defects. The NBDPS obtained information regarding potential maternal exposures through a comprehensive interview, and this allowed us to investigate numerous potential risk factors for biliary atresia. Secondly, there is a clear and consistent case definition for biliary atresia in the NBDPS, leading to a well-defined case group. The cases identified by the NBDPS were reviewed by a clinical geneticist at each site to ensure that the defects met the case definition of biliary atresia prior to interview. Subsequently, all cases identified were re-reviewed by one clinical geneticist (C. Moore) prior to analysis to ensure agreement of the diagnosis and classification of the cases. This careful classification might have helped identify associations between potential risk factors and the perinatal form of biliary atresia. However, previous dichotomization of biliary atresia into two forms based on the presence of additional congenital anomalies likely grouped infants with heterogeneous etiologies into the "embryonic" form and might have excluded infants from the "perinatal" form who had more common congenital anomalies (e.g., ventricular septal defects) that were unrelated to biliary atresia.

While this analysis provides support for previous reports of a possible association between seasonal variation and the occurrence of biliary atresia, more data are needed to evaluate whether the seasonal variation is a result of maternal infection. Additionally, future research should examine the role of nutrients in the development of biliary atresia. Research is particularly challenging because of the relatively low prevalence of biliary atresia. Despite this challenge, the morbidity and mortality associated with biliary atresia makes it essential that additional research be conducted to further explore infectious and non-infectious risk factors for biliary atresia.

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