
Association of maternal anemia with increased wheeze and asthma in children

Elizabeth W. Triche, PhD*; Lisbet S. Lundsberg, PhD†; Paige G. Wickner, MD‡; Kathleen Belanger, PhD†; Brian P. Leaderer, PhD†; and Michael B. Bracken, PhD†

Background: Increasing interest has focused on maternal nutrition and micronutrient status during pregnancy and respiratory disease development in the offspring.

Objective: To examine the relationship between maternal anemia in pregnancy with wheeze and asthma in early childhood.

Methods: The cohort included children of women followed through pregnancy and recontacted when the child was 6 years of age to evaluate respiratory health. Exposure was assessed using maternal anemia diagnosis and hemoglobin (Hgb) < 11 during delivery hospitalization. Study outcomes include wheezing in early childhood; patterns of wheeze from birth to age 6 (early-onset transient wheeze; late-onset wheeze; early-onset persistent wheeze); and diagnosis of childhood asthma.

Results: Maternal anemia was reported by 11.9% of mothers and was associated with recurrent infant wheeze in the first year (adjusted odds ratio [ORA] = 2.17, 95% confidence interval [CI] 1.18, 4.00), wheezing before age 3 (Ora = 2.42, 95% CI 1.38, 4.23), and early-onset transient and early-onset persistent wheeze patterns (Ora = 2.81, 95% CI 1.38, 5.72, and Ora = 2.07, 95% CI 1.02, 4.22), respectively. Among children of mothers with asthma, maternal anemia was associated with recurrent wheeze in year 1 (Ora = 4.22, 95% CI 1.65, 10.80) and wheeze before age 3 (Ora = 2.73, 95% CI 1.17, 6.35). Offspring of mothers with asthma also had increased odds of asthma diagnosis (Ora = 2.53, 95% CI 1.04, 6.17) and current asthma (Ora = 3.46, 95% CI 1.45, 8.26).

Conclusions: Maternal anemia during pregnancy is associated with infant respiratory health outcomes. If this observation is replicated, maternal anemia may be a target for intervention and future research.

Ann Allergy Asthma Immunol. 2011;106:131–139.

INTRODUCTION

Asthma and respiratory disease account for increasing childhood morbidity, placing a burden on the health care system and on affected individuals and families. In 2007, approximately 6.7 million children under the age of 18 had asthma,¹ with rates increasing to nearly 7 million (9.4%) by 2008.² As of 2008, more than 14% of children aged 0 to 17 years had been diagnosed with asthma,² with children 0 to 4 years of age demonstrating the greatest use of health care services for asthma-related illness.¹ Increases in childhood respiratory disease over the past decades have highlighted the need to identify specific factors associated with early childhood wheezing and childhood asthma. The rise in prevalence of asthma is too rapid to be attributable to genetic mutations,

and air pollution has actually declined in many areas where asthma rates have been increasing.

Recent research has suggested that maternal dietary factors during pregnancy may influence the development of childhood asthma.^{3,4} The intrauterine environment provides the substrate for many important processes, including lung and early immune system development, and support of optimal fetal growth requires adequate maternal nutritional status. Lung development in utero is apparent within 3 to 4 weeks after fertilization and continues throughout gestation and childhood.^{5,6} Inadequate nutritional status during gestation may negatively impact childhood respiratory health,^{3,4} particularly during critical periods of embryonic and fetal growth.

Maternal anemia, an indicator of overall nutritional status, has been linked to a number of adverse outcomes, including infant mortality, preterm delivery, poor gestational weight gain, low birth weight, and poor infant neurocognitive performance.^{7–9} Anemia is prevalent in the pregnant population in the United States (9.3% in the general pregnant population and up to 27% in low-income minority women^{7,8,10}; up to 95% of anemia in pregnancy is attributable to iron deficiency¹¹ resulting from inadequate iron intake or hemodilution of pregnancy).

Given the relatively high prevalence of maternal anemia in pregnancy, and its potential for influencing the respiratory health of offspring through fetal programming effects, further investigation into the role of maternal anemia on childhood respiratory outcomes is warranted. The current study examines the relation-

Affiliations: * Brown University, Department of Community Health/Epidemiology, Providence, RI; † Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale University, New Haven, CT; ‡ Section of Allergy and Clinical Immunology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT.

Disclosures: Michael Bracken and Paige Wickner work as occasional contractors for Pfizer, although the research in this paper is not related in any way to compensation received from this company. All other authors do not have any conflict of interest.

Funding Sources: This work was supported by grant # AI41040.

Received for publication August 9, 2010; Received in revised form October 29, 2010; Accepted for publication November 5, 2010.

© 2011 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.11.007

ship of maternal anemia in pregnancy with patterns of wheezing and asthma in early childhood.

METHODS

Study Population

The study population consists of families who participated in the Asthma in Pregnancy (AIP) Study and the Perinatal Risk of Asthma in Infants of Asthmatic Mothers Study. Methods have been described in detail previously^{12,13} (see Fig. 1 and eMethods). The current analysis was restricted to 597 families, with information available on childhood wheeze patterns, asthma diagnosis, maternal hemoglobin (Hgb) mea-

surements and International Statistical Classification of Diseases, 9th Revision (ICD-9) diagnosis of maternal anemia.

During the Asthma in Pregnancy study, pregnant women were interviewed in person, usually at home, before 24 weeks' gestation. A standardized interview collected information on demographic factors, pregnancy history, lifestyle risk factors (eg, body mass index [BMI], smoking, drug and alcohol use), asthma history, other medical conditions, and household characteristics. A postpartum interview was conducted during the delivery hospitalization or by telephone within 1 month of delivery to collect detailed information on asthma symptoms, medication use, and environmental expo-

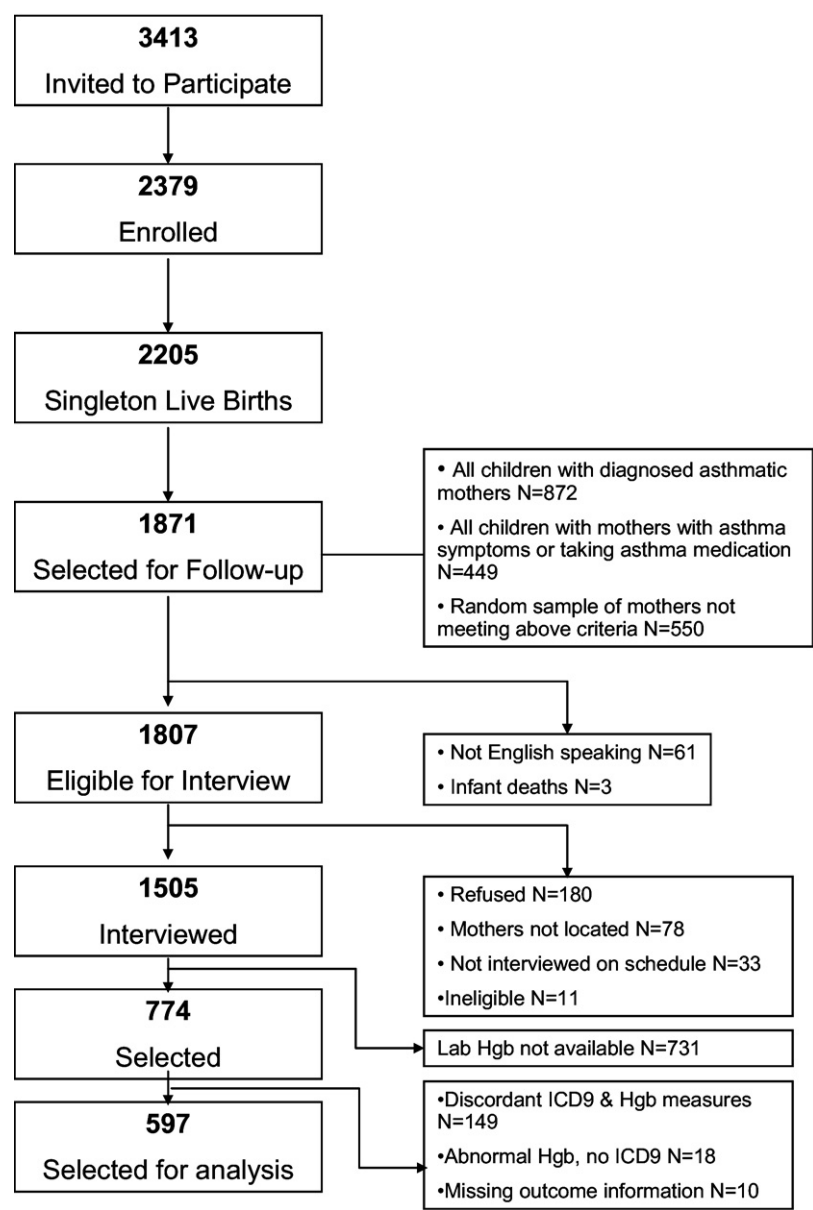


Figure 1. Recruitment into the Asthma in Pregnancy (AIP) study and the Perinatal Risks of Asthma in Infants of Asthmatic Mothers (PRAM) study.

tures during pregnancy. Medical records for the mother and infant were abstracted using a structured form for pregnancy outcome data, including prenatal, labor and delivery information, and information on the infant's birth weight, gestational age, and placement in a newborn intensive care unit (NICU).

Families were recontacted (Perinatal Risk of Asthma in Infants of Asthmatic Mothers) when the children were 6 years of age (± 3 months), and a standardized interview was administered in person with the child's primary caregiver, usually the mother. Information on the child's asthma history (symptoms, medication use, and diagnosis), early life exposures (eg, daycare attendance, breastfeeding, number of children in the household, exposure to tobacco smoking, mold, pets, gas stove use) were collected for the period from birth to age 6.

Written or oral consent was obtained from each participant per the guidelines of the local human investigations committee (or Institutional Review Board).

Exposure Assessment

Medical records were abstracted for evidence of maternal anemia during pregnancy. To be classified as having anemia, women had to have both (1) an ICD-9-CM code of 648.2 "Other current conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium: Anemia" and (2) maternal Hgb < 11 at the time of delivery hospitalization. This third trimester Hgb reference range is consistent with national/international guidelines.^{7,14}

Childhood Wheezing Assessment and Asthma Diagnosis

A structured interview administered by a trained research assistant at a home visit when the child was 6 years (± 3 months) of age elicited detailed information from the child's mother about the child's wheezing (including frequency) and asthma diagnosis. Wheeze outcomes for the analysis included recurrent wheeze (two or more episodes) in the first year of life and any wheeze by age 3. Information regarding onset, frequency, and duration were also used to classify wheeze patterns as *persistent* (symptoms still present in the previous 12 months at age 6) or *transient*, and *early* (≤ 3 years of age) or *late onset* as previously described by Martinez et al.¹⁵ Childhood asthma was based on maternal report of physician diagnosis of asthma; asthma outcomes for the current analysis included both *asthma diagnosis ever*, and *current asthma* defined as a physician diagnosis of asthma plus wheeze or medication use during the previous 12-month period.

Data analysis

Statistical analyses examined associations between maternal anemia and childhood respiratory outcomes, including (1) recurrent wheeze in the first year of life; (2) wheeze by age 3; (3) asthma diagnosis ever; (4) current asthma; and (5) patterns of wheeze in infancy and early childhood. Unadjusted associations between maternal anemia and each of the outcomes were examined using χ^2 tests. Separate logistic regression models were run for each of the dichotomous outcomes

(recurrent 1st year wheeze, wheeze by age 3, asthma diagnosis ever, and current asthma). Multinomial logistic regression models were fit for the polytomous outcome of childhood wheeze pattern (no wheeze, early-onset transient, late-onset, and early-onset persistent). Additional analyses stratified the cohort by maternal asthma status. Final models were constructed using backward elimination, including exposures of interest and potential confounders. Potential confounders included sex, maternal race/ethnicity, number of children in the household, maternal asthma diagnosis, allergies, education, prepregnancy BMI, smoking in pregnancy, folate supplementation in first trimester, NICU placement at birth, preterm delivery (< 37 weeks' gestation from last menstrual period), intrauterine growth restriction, number of months breastfed, and environmental exposures in the first and fifth years of life (smoking in household, pets in home, mold in home, gas stove use in home), and daycare attendance (1st year). All potential confounders were retained in the final models. Because of the strong differential genetic risk that maternal asthma status confers for childhood outcomes, we also stratified analyses by maternal asthma diagnosis. PC-SAS version 9.1 software was used for statistical analysis.

RESULTS

Table 1 presents population characteristics by maternal anemia status, recurrent wheeze in year 1, and current asthma for the cohort ($n = 597$). Slightly over half of the children were male (53%), and 76% were white, non-Hispanic. Mothers with asthma were, by design, overselected for the study (44% of the cohort had asthma), and an even greater frequency reported maternal allergies (67%). Frequencies of NICU placement at birth (18%), preterm delivery (9%) and intrauterine growth restriction (7%) were typical for this population. During the first year of life, 5% reported smoking in the household, 33% of infants were in daycare, 56% had pets in the home, and 15% reported mold in the home.

Overall, 11.9% of the mothers were identified through medical record abstraction as having maternal anemia in pregnancy. Among their children, 22% had recurrent wheeze in year 1, and 17% had active asthma at age 6 (physician-diagnosed asthma plus wheeze or medication use in the past year). Women with African-American and Hispanic children, with lower education, and with lower folate supplementation during the first trimester of pregnancy were more likely to have anemia in pregnancy; in addition, their children were more likely to have recurrent year 1 wheeze and active asthma at age 6. Maternal smoking in pregnancy, not breastfeeding, and having no pets in the home were also associated with maternal anemia. Recurrent wheeze in the first year of life was more frequent among children of mothers with asthma, higher prepregnancy BMI, NICU placement, preterm delivery, shorter duration of breastfeeding, daycare in the first year of life, and mold in the home. The child's sex, having only one child in the household, maternal asthma and allergies, NICU placement, and having no pets in the home were associated with active asthma at age 6.

Table 1. Associations Between Population Characteristics, Maternal Anemia, Childhood Wheeze, and Asthma Diagnosis

	Total N ^a	% with maternal anemia in pregnancy	P-value	Childhood respiratory outcomes			
				% Recurrent wheeze year 1	P-value	% Active asthma at age 6	P-value
Overall	597	11.9		22.1		17.2	
Child's sex			.55		.38		.03
Male	314	11.2		23.5		20.4	
Female	283	12.7		20.5		13.8	
Child's race/ethnicity			<.0001		<.001		<.0001
White	452	8.0		18.5		13.1	
African-American	43	30.2		38.1		25.6	
Hispanic	47	29.8		39.1		42.6	
Biracial	54	14.8		22.6		24.1	
No. of children in household			.08		.56		.04
1 Child	91	12.1		19.1		26.4	
2 Children	296	9.1		23.9		16.2	
3 or More children	210	15.7		20.9		14.8	
Maternal asthma			.08		<.001		<.0001
No	336	9.8		17.0		11.9	
Yes	261	14.6		28.6		24.1	
Maternal allergies			.39		.55		.007
No	195	10.3		23.6		11.3	
Yes	402	12.7		21.4		20.2	
Maternal education			.01		.009		.0007
< High school	50	24.0		39.6		30.0	
High school graduate	80	15.0		26.6		16.2	
Some college	151	16.6		21.8		22.5	
College graduate	155	6.5		21.9		18.7	
> College	159	7.6		15.3		7.5	
Maternal pre-pregnancy body mass index (BMI)			.56		.03		.38
Underweight	61	14.8		18.3		21.3	
Normal weight	326	10.4		18.4		15.0	
Overweight	64	15.6		33.9		15.6	
Obese	141	12.8		25.5		20.6	
Maternal smoking in 1st trimester of pregnancy			.008		.06		.13
No	515	10.5		20.8		16.3	
Yes	82	20.7		30.4		23.2	
Folate supplementation			<.0001		.002		.01
<270	119	26.1		33.6		26.1	
270 to <500	121	10.7		25.2		19.0	
500 to <700	155	9.7		18.8		14.2	
700 or higher	197	6.1		15.8		12.7	
Neonatal intensive care unit (NICU) placement			.14		.001		.01
No	492	12.8		19.5		15.4	
Yes	105	7.6		34.0		25.7	
Preterm delivery			.93		.003		.12
No	545	11.9		20.5		16.5	
Yes	52	11.5		38.5		25.0	
Small for gestational age (SGA)			.71		.10		.85
No	552	11.8		21.1		17.0	
Yes	44	13.6		31.8		18.2	
Breastfeeding (# months)			.02		.001		.23
None	183	18.6		28.9		20.2	
1-3	107	9.4		20.9		20.6	
4-6	92	8.7		30.0		18.5	
7-12	125	8.8		16.0		13.6	
>12	90	8.9		10.0		11.1	

Table 1. (Continued) Associations Between Population Characteristics, Maternal Anemia, Childhood Wheeze, and Asthma Diagnosis

	Total N ^a	% with maternal anemia in pregnancy	P-value	Childhood respiratory outcomes			
				% Recurrent wheeze year 1	P-value	% Active asthma at age 6	P-value
Household smoking—yr 1			.19		.34		.75
No	566	11.5		21.7		17.1	
Yes	31	19.4		29.0		19.4	
Household smoking—yr 5			.28		.53		.32
No	563	11.5		21.8		16.9	
Yes	34	17.6		26.5		23.5	
Day care—yr 1			.63		.002		.88
No	400	11.5		18.4		17.5	
Yes	194	12.9		29.5		17.0	
Pets in home—yr 1			<.0001		.45		.01
No	264	17.8		23.5		21.6	
Yes	333	7.2		20.9		13.8	
Pets in home—yr 5			<.0001		.54		.01
No	225	18.7		23.4		22.2	
Yes	372	7.8		21.3		14.2	
Mold in home—yr 1			.65		.74		.66
No	506	11.7		21.9		17.0	
Yes	90	13.3		23.5		18.9	
Mold in home—yr 5			.82		.03		.34
No	473	12.1		20.1		16.5	
Yes	124	11.3		29.5		20.2	

^a Ns may not add up to the total because of missing values.

Table 2 presents unadjusted associations between maternal anemia, early childhood wheeze, and asthma outcomes. Women with maternal anemia were more likely to have infants with recurrent wheeze in the first year of life compared with mothers without anemia (odds ratio [OR] = 2.52, 95% CI 1.50, 4.23);

Table 2. Unadjusted Associations Between Maternal Anemia and Childhood Respiratory Outcomes

Outcome	N	Maternal anemia ^a		OR	95% CI
		No	Yes		
Shorter-term outcomes					
Year 1 recurrent wheeze					
No	462	417	45	1.00	
Yes	131	103	28	2.52	1.50, 4.23
Wheeze before age 3					
No	368	338	30	1.00	
Yes	230	189	41	2.44	1.48, 4.04
Longer-term outcomes					
Asthma diagnosis—ever					
No	486	437	49	1.00	
Yes	119	94	25	2.37	1.39, 4.03
Asthma diagnosis + wheeze or med use at age 6					
No	501	451	50	1.00	
Yes	106	82	24	2.64	1.54, 4.53

^a Maternal anemia defined as measured hemoglobin ≤ 11 at time of delivery hospitalization + indication in medical chart that patient was diagnosed with anemia.

similarly, odds of wheezing before age 3 among children born to mothers with anemia was significantly elevated compared with non-anemic mothers (OR = 2.44, 95% CI 1.48, 4.04). Maternal anemia was also associated with their child's asthma; mothers anemic during pregnancy were more likely to have a child ever diagnosed with asthma (OR = 2.37, 95% CI 1.39, 4.03), and a child with asthma at age 6 (OR = 2.64, 95% CI 1.54, 4.53) than non-anemic women.

Results of adjusted logistic regression models are presented in Table 3. Maternal anemia remained significantly associated with recurrent wheeze during the 1st year of life (adjusted odds ratio [ORa] = 2.11, 95% CI 1.12, 3.98), as well as wheeze before age 3 (ORa = 2.36, 95% CI 1.34, 4.17). After adjustment for confounders, associations between maternal anemia and asthma outcomes were attenuated: odds of asthma diagnosis ever (ORa = 1.60, 95% CI 0.83, 3.07) and asthma at age 6 (ORa = 1.76, 95% CI 0.90, 3.43) were nonsignificantly higher among children born to anemic mothers.

Among mothers with asthma, maternal anemia remained significantly associated with increased odds of recurrent wheeze in the first year (ORa = 4.78, 95% confidence interval [CI] 1.75, 13.08), wheeze by age 3 (ORa = 2.83, 95% CI 1.19, 6.75), asthma diagnosis ever (ORa = 2.98, 95% CI 1.21, 7.34), and current asthma (ORa = 3.80, 95% CI 1.52, 9.53). Among mothers without asthma, maternal anemia remained associated with wheeze before age 3 (ORa = 2.58, 95% CI 1.10, 6.05).

Among all children, maternal anemia was associated with a nearly 3-fold increase in odds of early onset transient

Table 3. Adjusted^a Odds Ratios of Associations Between Maternal Anemia and Respiratory Health Outcomes, All Children Combined and Stratified by Maternal Asthma Status

Outcome	All children		Nonasthmatic mothers		Asthmatic mothers	
	ORa	95% CI	ORa	95% CI	ORa	95% CI
Shorter-term outcomes						
Year 1 recurrent wheeze	2.11	1.12–3.98	1.64	0.58–4.61	4.78	1.75–13.08
Wheeze before age 3	2.36	1.34–4.17	2.58	1.10–6.05	2.83	1.19–6.75
Longer-term outcomes						
Asthma diagnosis—ever	1.60	0.83–3.07	0.77	0.21–2.78	2.98	1.21–7.34
Asthma diagnosis + wheeze or med use at age 6	1.76	0.90–3.43	0.66	0.17–2.57	3.80	1.52–9.53

^a Adjusted for child's sex, race, # children in household at age 6, maternal allergies, maternal education, pre-pregnancy BMI, maternal smoking in 1st trimester, folate supplementation in first trimester, NICU admission, preterm delivery, SGA, # months breastfed, smoking in household in years 1 and 5, daycare attendance in year 1, pets in years 1 and 5, mold in years 1 and 5.

wheeze (ORa = 2.76, 95%CI 1.35, 5.64) but not late-onset wheezing (ORa = 0.77, 95% CI 0.22, 2.65) (Table 4). Early-onset persistent wheezing in children of mothers with anemia increased twofold (ORa = 1.96, 95% CI 0.95, 4.03). Stratified by maternal asthma status, maternal anemia remained associated with increased odds of early-onset transient wheeze for children of mothers who did not have asthma (ORa = 3.90, 95% CI 1.43, 10.6), but the association was attenuated among mothers with asthma (ORa = 2.56, 95% CI 0.77, 8.50). Too few observations were available to estimate the association for late-onset wheezing among offspring of mothers without asthma, and there was no association of anemia in mothers with asthma with children's late-onset wheezing (ORa = 0.72, 95% CI 0.11, 4.60). The association between anemia and early-onset persistent wheeze was more pronounced among mothers with asthma (ORa = 3.67, 95% CI: 1.27, 10.6) than among mothers without asthma (ORa = 1.18, 95% CI: 0.35, 4.04).

DISCUSSION

Maternal anemia during pregnancy was associated with both short-term (recurrent wheeze in first year of life and wheeze

by 3 years of age) and longer-term (asthma diagnosis ever and asthma at age 6) respiratory health outcomes in children. Maternal asthma status appears to modify these associations. Among mothers with asthma, maternal anemia is associated with an increase in odds of more persistent respiratory outcomes, including asthma and persistent wheeze in the children at age 6. Among mothers without asthma, maternal anemia was more strongly associated with shorter-term respiratory outcomes in the children.

Results reported here for wheeze complement and extend the findings of a previous investigation examining the effect of in utero iron exposure and early wheeze, in which cord iron levels were inversely related to early childhood wheezing, OR = 0.86, 95% CI 0.75, 0.99 per doubling of iron concentration.¹⁶ Infants born to mothers with anemia may have normal iron levels because of active placental iron transport; however, levels are typically lower than those in infants born to mothers without anemia.^{17–19} Associations between maternal anemia and early life respiratory outcomes (particularly 1st year of life) may be expected to be strongest because exposures to iron stores from pregnancy typically last only through the first 6 months of life.^{20,21} However, as

Table 4. Adjusted Associations Between Maternal Anemia and Childhood Wheeze Patterns, All Children Combined and by Maternal Asthma Status^a

Wheeze pattern ^b	All children		Nonasthmatic mothers		Asthmatic mothers	
	ORa	95% CI	ORa	95% CI	ORa	95% CI
No wheeze	Ref		Ref		Ref	
Early-onset, transient	2.76	1.35–5.64	3.90	1.43–10.6	2.56	0.77–8.50
Late-onset	0.77	0.22–2.65		NAC ^c	0.72	0.11–4.60
Early-onset, persistent	1.96	0.95–4.03	1.18	0.35–4.04	3.67	1.27–10.6

^a Adjusted for child's sex, race, number of children in household at age 6, maternal allergies, maternal education, pre-pregnancy body mass index, maternal smoking in 1st trimester, folate supplementation in first trimester, neonatal intensive care unit admission, preterm delivery, small for gestational age, number of months breastfed, smoking in household in years 1 and 5, daycare attendance in year 1, pets in years 1 and 5, mold in years 1 and 5.

^b Early-onset transient wheeze = wheeze onset <3 years but no symptoms by age 6; late-onset wheeze = wheeze ≥3 years; early-onset persistent wheeze = wheeze <3 years and wheeze at age 6.

^c NAC (not able to calculate).

found in our study, the effects of in utero exposures could persist longer than the first year of life.^{22–24} Our observation that associations between anemia and childhood wheeze differ based on maternal asthma status suggests that programming effects of maternal nutritional status on the child's respiratory health may be particularly important among children with a genetic predisposition for asthma. Associations of maternal anemia with respiratory outcomes and childhood asthma may be indicative of fetal programming or childhood nutritional status.

A US study found nonhereditary, nonhemolytic anemia to be the most common complication of pregnancy, with rates around 9.3%,¹⁰ in accord with the prevalence rate in this study. However, among low-income minority populations in the United States, iron-deficiency anemia is approximately 27% in the third trimester.^{7,8} Even in the United States, where anemia rates are relatively low and severe anemia is quite rare compared with developing countries, with rates as high as 73% reported,²⁵ this study was able to document associations with respiratory health.

Objective measure of maternal anemia was a major strength of this study. Comprehensive assessment of maternal anemia at the time of delivery, using both ICD-9 codes and laboratory values of Hgb, significantly reduced the potential for exposure misclassification. However, the underlying cause of the anemia (eg, inadequate dietary iron intake, dilution caused by a large increase in plasma volume in pregnancy, impaired absorption) was not ascertained. We used an Hgb cutoff of <11 to classify maternal anemia, which is appropriate for the third trimester of pregnancy and has been used to define anemia in pregnancy^{26–28}; the cutoff of 11, compared with the cutoff of 12 typically used to indicate anemia in nonpregnant women, accounts at least in part for some level of dilution that is normal in pregnancy.

Another strength was the ability to control numerous potentially important confounding variables, including folate supplementation, many of which were assessed prospectively with respect to the respiratory outcomes. These factors could potentially explain the association of maternal anemia with respiratory outcomes, yet the overall conclusions were relatively unchanged after adjustment in logistic regression modeling. The robust sample size ($n = 597$), together with the overrepresentation of asthmatic mothers, allowed for examination of modifying effects by maternal asthma status.

Some limitations should be considered. Because of the time elapsed between information ascertainment at age 6 and symptoms in the first year of life, there may be recall error for the short-term respiratory outcomes. The current analysis is based on medical reports of anemia and assumes iron deficiency based on clinical diagnosis. However, medical charts are not expected to be differentially influenced by recall, and nondifferential recall would force the risk estimate toward the null. Moreover, the hypothesis of anemia and asthma would not be familiar to physicians, patients, or research staff, making ascertainment bias unlikely. Associations between anemia and longer-term outcomes based on current respira-

tory symptoms are less likely to be affected by inaccurate reporting.

Another potential limitation was the availability of Hgb levels at time of delivery on only a subset of the larger cohort of 1,505 women. We considered the possibility that missing Hgb could be related to our study outcomes. However, availability of Hgb in our study was unrelated to subsequent childhood asthma and respiratory symptom outcomes in our study. We chose the more specific rather than sensitive measure of exposure, and only classified women who met both criteria (ICD-9 diagnosis of anemia at some point in pregnancy and Hgb < 11 at time of delivery) as having maternal anemia. As a sensitivity analysis, we repeated study analyses redefining maternal anemia as an ICD-9 code noted at any point in the patient's medical record. Although the conclusions were consistent with those using the more specific measure, the associations were attenuated, most likely because of nondifferential misclassification. For example, the less specific measure included women who may have been anemic and successfully treated early in pregnancy with less chance of affecting the fetus.

Because the literature in this area is limited, specific biological mechanisms to explain the association between maternal anemia and respiratory symptoms are unclear. Maternal anemia is an indicator of general nutritional status and thus may be a proxy for a specific causal agent. For example, other micronutrients have been identified in the development of infant susceptibility to respiratory disease, including: selenium,^{16,29} maternal vitamin D,³⁰ and vitamin C,³¹ zinc,^{32,33} vitamin E,^{32–34} and folic acid.^{35,36} Although we did not have data on specific micronutrient intake, we were able to adjust for folate supplementation during the first trimester of pregnancy. Whereas folate supplementation was associated with maternal anemia, associations between maternal anemia and respiratory outcomes were not substantially changed when folate was included in the models. The association of folic acid supplementation in this study has been analyzed in detail elsewhere, and no evidence was found for an association with asthma risk in children aged 6 years.³⁷ Folic acid supplementation therefore was not a confounding factor in this analysis of maternal anemia.

Iron deficiency, the single most common cause of maternal anemia in pregnancy, may directly impact childhood respiratory health. Dietary changes have been substantial during the past few decades.^{38,39} Analysis of the National Health and Nutrition Examination Survey data showed improvements in iron intake during 1971 to 2000 among males and children; however, iron-deficient anemia has increased for low-income women of childbearing age and is highest in prevalence among minority females.⁴⁰ Iron intake continues to be low for female adolescents, in both the United States and Europe, despite increased total energy intake since the 1960s.^{41,42} Previous research has demonstrated an increased risk between high serum iron and asthma^{43–45}; however, these were retrospective investigations of adult or childhood iron levels, rather than in utero exposures.

Further research is needed to confirm these findings and to understand how maternal anemia may influence childhood respiratory health. Identification of such mechanisms may lead to targeted interventions to reduce the burden of childhood respiratory disease, particularly in those born to women with asthma. Cohort studies investigating iron levels, other nutritional biomarkers, and dietary patterns, from in utero throughout childhood, will be critical to understanding the long-term effects of nutritional status on risk of respiratory disease.

REFERENCES

- Akinbami, LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980–2007. *Pediatrics*. 2009;123(Suppl 3):S131–S145.
- Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2007. *Vital Health Stat*. 2009;10:1–80.
- Pali-Scholl I, Renz H, Jensen-Jarolim E. Update on allergies in pregnancy, lactation, and early childhood. *J Allergy Clin Immunol*. 2009; 123:1012–1021.
- Devereux G. Early life events in asthma: diet. *Pediatr Pulmonol*. 2007; 42:663–673.
- Burri PH. Structural aspects of prenatal and postnatal development and growth of the lung. In: McDonald JA, ed. *Lung Growth and Development*. New York, NY: Marcel Dekker, 1997.
- Joshi S, Kotecha S. Lung growth and development. *Early Hum Dev*. 2007;83:789–794.
- ACOG. ACOG Practice Bulletin No. 95: anemia in pregnancy. *Obstet Gynecol*. 2008;112:201–207.
- Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. *Am J Clin Nutr*. 2005;81:1218S–1222S.
- Keen CL, Clegg M, Hanna L, et al. The plausibility of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications. *J Nutr*. 2003;133:1597S–1605S.
- Bruce FC, Berg CJ, Hombrook MC, et al. Maternal morbidity rates in a managed care population. *Obstet Gynecol*. 2008;111:1089–1095.
- Merck Manuals Online. *Anemia in Pregnancy*. 2008 [cited July 27, 2009; Available at: <http://www.merck.com/mmpe/sec18/ch261/ch261b.html>. Accessed November 16, 2010].
- Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol*. 2009;114: 1295–1306.
- Bracken M, Triche E, Belanger K, Saftlas A, Beckett W, Leaderer B. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. *Obstet Gynecol*. 2003;102:739–752.
- World Health Organization. *Iron Deficiency Anaemia: Assessment, Prevention and Control*. 2001.
- Martinez F, Wright A, Taussig L, et al. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332:133–138.
- Shaheen S, Newson R, Henderson A, et al. Umbilical cord trace elements and minerals and risk for early childhood wheezing and eczema. *Eur Respir J*. 2004;24:292–297.
- Milman N. Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy. *Int J Hematol*. 1996; 63:103–135.
- Allen LH. Anemia and iron deficiency: effects on pregnancy outcome. *Am J Clin Nutr*. 2000;71(Suppl):12880S–12884S.
- Jaime-Perez JC, Herrera-Garza JL, Gomez-Almaguer D. Sub-optimal fetal iron acquisition under a maternal environment. *Arch Med Res*. 2005;36:598–602.
- Siimes MA, Addiego JE, Jr., Dallman PR. Ferritin in serum: diagnosis of iron deficiency and iron overload in infants and children. *Blood*. 1974;43:581–590.
- Hay G, Refsum H, Whitelaw A, Melbye EL, Haug E, Borch-Iohnsen B. Predictors of serum ferritin and serum soluble transferrin receptor in newborns and their associations with iron status during the first 2 y of life. *Am J Clin Nutr*. 2007;86:64–73.
- Barker DJ. A new model for the origins of chronic disease. *Med Health Care Philos*. 2001;4:31–35.
- Mathers JC. Early nutrition: impact on epigenetics. *Forum Nutr*. 2007; 60:42–48.
- Burdge GC, Hanson MA, Slater-Jefferies JL, Lillycrop KA. Epigenetic regulation of transcription: a mechanism for inducing variations in phenotype (fetal programming) by differences in nutrition during early life? *Br J Nutr*. 2007;97:1036–1046.
- Pathak P, Kapil U, Kapoor SK, et al. Prevalence of multiple micronutrient deficiencies amongst pregnant women in a rural area of Haryana. *Ind J Pediatr*. 2004;71:1007–1014.
- Kumar A, Rai AK, Basu S, Dash D, Singh JS. Cord blood and breast milk iron status in maternal anemia. *Pediatrics*. 2008;121:673–677.
- Brion MJ, Leary SD, Smith GD, McArdle HJ, Ness AR. Maternal anemia, iron intake in pregnancy, and offspring blood pressure in the Avon Longitudinal Study of Parents and Children. *Am J Clin Nutr*. 2008;88:1126–1133.
- Kilbride J, Baker TG, Parapia LA, Khoury SA, Shuqaidef SW, Jerwood D. Anaemia during pregnancy as a risk factor for iron-deficiency anaemia in infancy: a case-control study in Jordan. *Int J Epidemiol*. 1999; 28:461–468.
- Devereux G, McNeill G, Turner S, et al. Early childhood wheezing symptoms in relation to plasma selenium in pregnant mothers and neonates. *Clin Exp Allergy*. 2007;37:1000–1008.
- Devereux G, Lionjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr*. 2007; 85:853–859.
- Martindale S, McNeill G, Devereux G, Campbell D, Russell G, and Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am J Respir Crit Care Med*. 2005;171:121–128.
- Devereux G, Turner SW, Craig LC, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med*. 2006;174:499–507.
- Litonjua AA, Rifas-Shiman SL, Ly NP, et al. Gold, Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 y of age. *Am J Clin Nutr*. 2006;84:903–911.
- Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am J Respir Crit Care Med*. 2005;171: 121–128.
- Haberg SE, London SJ, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. *Arch Dis Child*. 2009;94:180–184.
- Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. *Am J Epidemiol*. 2009;170:1486–1493.
- Martinussen M, Risnes K, Jacobsen G, Bracken M. No increased risk for asthma in children aged six observed among mothers who used folic acid supplementation in early pregnancy. Under Review.
- Chanmugam P, Guthrie JF, Cecilio S, Morton JF, Basiotis PP, Anand R. Did fat intake in the United States really decline between 1989–1991 and 1994–1996? *J Am Diet Assoc*. 2003;103:867–872.
- Nielsen SJ, Siega-Riz AM, Popkin BM. Trends in energy intake in U.S. between 1977 and 1996: similar shifts seen across age groups. *Obes Res*. 2002;10:370–378.
- Briefel RR, Johnson CL. Secular trends in dietary intake in the United States. *Annu Rev Nutr*. 2004;24:401–431.
- Cavadini C, Siega-Riz AM, Popkin BM. US adolescent food intake trends from 1965 to 1996. *West J Med*. 2000;173:378–383.
- Cruz JA. Dietary habits and nutritional status in adolescents over Europe–Southern Europe. *Eur J Clin Nutr*. 2000;54(Suppl 1):S29–S35.

-
43. Kocyigit A, Armutcu F, Gurel A, Ermis B. Alterations in plasma essential trace elements selenium, manganese, zinc, copper, and iron concentrations and the possible role of these elements on oxidative status in patients with childhood asthma. *Biological Trace Element Res.* 2004;97:31–41.
44. Narula MK, Ahuja GK, Whig J, Narang AP, Soni RK. Status of lipid peroxidation and plasma iron level in bronchial asthmatic patients. *Indian J Physiol Pharmacol.* 2007;51:289–292.
45. Ekmekci OB, Donma O, Sardogan E, et al. Iron, nitric oxide, and myeloperoxidase in asthmatic patients. *Biochemistry (Mosc).* 2004;69: 462–467.

Requests for reprints should be addressed to:
Corresponding Author and Request for Reprints:
Elizabeth W. Triche
Brown University
Department of Community Health/Epidemiology
Box G-S121-2
121 S. Main St.
Providence, RI 02912
E-mail: Elizabeth_triche@brown.edu

Answers to CME examination—*Annals of Allergy, Asthma & Immunology*, February 2011 Sacha JJ: The environment, the airway, and the athlete. *Ann Allergy Asthma Immunol.* 2010;106:81–88.

1. d
2. e
3. e
4. e
5. d

E-METHODS

The study population consists of families who participated in the Asthma in Pregnancy (AIP) Study and the Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM) Study. Between April 1997 and June 2000, pregnant women were recruited from 54 private obstetrical practices and 15 hospital and community-based prenatal care clinics delivering at one of six participating hospitals in Connecticut and one hospital in south central Massachusetts into the prospective Asthma in Pregnancy (AIP) cohort study. Of the 3,413 eligible women who were <24 weeks gestational age at enrollment, 2,379 women enrolled in the study of whom 2,205 had a singleton live birth. Women were followed through delivery and medical records were abstracted. From September 2003 through January 2007, a follow-up study, Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM), was conducted on a subgroup of the children born to these women to determine the genetic and perinatal risk factors associated with asthma development. Of the 2,205 women in the AIP study who

delivered a singleton live birth, 1,871 were selected and 1,807 were eligible for participation in PRAM based on their asthma status. All children whose mothers had an asthma diagnosis ($n = 872$) or had symptoms or took asthma medications during pregnancy ($n = 449$) were invited to participate in the follow-up study when the child was about six years of age, along with a random sample of children whose mothers did not have a history of asthma diagnosis or symptoms/medication use during pregnancy ($n = 550$). A total of 1,505 (83.3%) enrolled, 180 refused (mainly due to requirement to provide DNA), 78 could not be located, 33 could not be interviewed on schedule, and 11 were ineligible. A total of 774 women had lab hemoglobin (Hgb) values taken at time of delivery available in medical records. Families with an ICD9 diagnosis of anemia but normal Hgb measurements ($n = 149$), those with abnormal Hgb measurements but no ICD9 diagnosis of anemia ($n = 18$), and those without wheezing or childhood asthma information ($n = 10$), were excluded from the analysis.