Published in final edited form as:
Ann Allergy Asthma Immunol. 2011 February ; 106(2): 131–139.e1. doi:10.1016/j.anai.2010.11.007.

Association of maternal anemia with increased wheeze and asthma in children

Elizabeth W. Triche, Ph.D.,
Brown University, Department of Community Health/Epidemiology, Providence, RI

Lisbet S. Lundsberg, Ph.D.,
Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale University, New Haven, CT

Paige G. Wickner, M.D.,
Section of Allergy and Clinical Immunology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT

Kathleen Belanger, Ph.D.,
Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale University, New Haven, CT

Brian P. Leaderer, Ph.D., and
Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale University, New Haven, CT

Michael B. Bracken, Ph.D.
Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale University, New Haven, CT

Keywords

Respiratory symptoms; wheeze; asthma; maternal anemia

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 0–17 had been diagnosed with asthma [2], with children 0–4 years 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

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, Tel: 401 863-1987, Fax: 401 863-3713, Elizabeth_triche@brown.edu.

Conflict of Interest: 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.

early childhood wheezing and childhood asthma. The rise in prevalence of asthma is too rapid to be due 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 3–4 weeks after fertilization and continues throughout gestation and childhood[5].[6] It is possible, then, that 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 4 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 deficiency[11] resulting from inadequate iron intake and/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 relationship 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 (PRAM) Study. Methods have been described in detail previously[12,13] (see Figure 1 and eMethods) The current analysis was restricted to 597 families with information available on childhood wheeze patterns, asthma diagnosis, maternal Hgb measurements and ICD9 diagnosis of maternal anemia.

During the AIP study, pregnant women were interviewed in-person, usually at home, before 24 weeks gestation. A standardized interview collected information on demographic factors, pregnancy history, life-style risk factors (e.g., 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 one month of delivery to collect detailed information on asthma symptoms, medication use, and environmental exposures 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 birthweight, gestational age, and placement in a newborn intensive care unit (NICU).

Families were re-contacted (PRAM) when the children were six 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 (e.g., 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 six.

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

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 hemoglobin (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 six 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 six) or *transient*, and *early* (≤3 years of age) or *late onset* as previously described by Martinez[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 three, 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: gender, maternal race/ethnicity, number of children in the household, maternal asthma diagnosis, allergies, education, pre-pregnancy BMI, smoking in pregnancy, folate supplementation in first trimester, NICU placement at birth, preterm delivery (<37 weeks gestation from LMP), intrauterine growth restriction (IUGR), 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, over-selected 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 pre-pregnancy BMI, NICU placement, preterm delivery, shorter duration of breastfeeding, daycare in the first year of life, and mold in the home. Child gender, 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 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 to mothers without anemia (OR=2.52, 95% CI 1.50, 4.23); similarly, odds of wheezing before age 3 among children born to mothers with anemia was significantly elevated compared to 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 (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 non-significantly higher among children born to anemic mothers.

Among asthmatic mothers, maternal anemia remained significantly associated with increased odds of recurrent wheeze in the first year (ORa=4.78, 95% 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 non-asthmatic mothers, 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 three-fold increase in odds of early onset transient 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 two-fold (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 non-asthmatic mothers (ORa=3.90, 95% CI 1.43, 10.6), but the association was attenuated among asthmatic mothers (ORa=2.56, 95% CI 0.77, 8.50). There were too few observations to estimate the association for late onset wheezing among offspring of non-asthmatic mothers, and there was no association of anemia in asthmatic mothers 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 asthmatic mothers (ORa=3.67, 95% CI: 1.27, 10.6) than among non-asthmatic mothers (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 asthmatic mothers, 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 non-asthmatic mothers, 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, where 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 non-anemic mothers[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 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 on respiratory outcomes and childhood asthma may be indicative of fetal programming or childhood nutritional status.

A US study found nonhereditary, non-hemolytic 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 to 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 (e.g., inadequate dietary iron intake, dilution due to large increase in plasma volume in pregnancy, impaired absorption) was not ascertained. We utilized Hgb cut-off 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 to the cutoff of 12 typically used to indicate anemia in non-

pregnant 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 on respiratory outcomes, yet the overall conclusions were relatively unchanged following 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.

There are some limitations that 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 non-differential 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 respiratory 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 1505 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. While the conclusions were consistent with those using the more specific measure, the associations were attenuated, most likely due to non-differential 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.

As 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]. While we did not have data on specific micronutrient intake, we were able to adjust for folate supplementation during the first trimester of pregnancy. While 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 six.[37]. Folic acid supplementation was not, therefore, a confounding factor in this analysis of maternal anemia.

It is also possible that 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 NHANES data showed

improvements in iron intake during 1971–2000 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, both in the US and Europe, despite increased total energy intake since the 1960's[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.

Acknowledgments

Sources of Financial Support: This work was supported by grant # AI41040

Biographies

Elizabeth Triche conceived of the research idea, was co-Investigator on the grant that collected the original data, analyzed the data, wrote the methods and results, and provided critical feedback and guidance for the introduction/background and the discussion.

Lisbet Lundsberg wrote sections of the introduction and discussion, was involved in substantial revisions of the original manuscript, and provided critical feedback on the methods and results.

Paige Wickner provided critical feedback on all sections of the manuscript, particularly the clinical interpretation of the findings. She was involved in substantial revisions and editing of the manuscript.

Kathleen Belanger was co-Investigator on the grant that collected the original data and critically reviewed the manuscript.

Brian Leaderer was co-Investigator on the grant that collected the original data and critically reviewed the manuscript

Michael Bracken was Principal Investigator on the grant that collected the original data, provided valuable feedback on the analysis and interpretation of results, and critically reviewed the manuscript.

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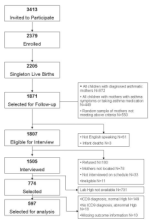

Figure 1.
AIP/PRAM Study Cohort

Ann Allergy Asthma Immunol. Author manuscript; available in PMC 2012 February 1.

Table 1

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

				Childhood Respiratory Outcomes			
	Total N[1]	**% with maternal anemia in pregnancy**	**P-value**	**% Recurrent wheeze year 1**	**P-value**	**% active asthma at age 6**	**P-value**
Overall	597	11.9		22.1		17.2	
Child gender			0.55		0.38		0.03
Male	314	11.2		23.5		20.4	
Female	283	12.7		20.5		13.8	
Child's race/ethnicity			<0.0001		<0.001		<0.0001
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	
# of children in household			0.08		0.56		0.04
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			0.08		<0.001		<0.0001
No	336	9.8		17.0		11.9	
Yes	261	14.6		28.6		24.1	
Maternal allergies			0.39		0.55		0.007
No	195	10.3		23.6		11.3	
Yes	402	12.7		21.4		20.2	
Maternal education			0.01		0.009		0.0007
< 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	

				Childhood Respiratory Outcomes			
	Total N[1]	**% with maternal anemia in pregnancy**	**P-value**	**% Recurrent wheeze year 1**	**P-value**	**% active asthma at age 6**	**P-value**
Maternal pre-pregnancy body mass index (BMI)			0.56		0.03		0.38
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			0.008		0.06		0.13
No	515	10.5		20.8		16.3	
Yes	82	20.7		30.4		23.2	
Folate supplementation			<0.0001		0.002		0.01
<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	
NICU placement			0.14		0.001		0.01
No	492	12.8		19.5		15.4	
Yes	105	7.6		34.0		25.7	
Preterm delivery			0.93		0.003		0.12
No	545	11.9		20.5		16.5	
Yes	52	11.5		38.5		25.0	
Small for gestational age (SGA)			0.71		0.10		0.85
No	552	11.8		21.1		17.0	
Yes	44	13.6		31.8		18.2	
Breastfeeding (# months)			0.02		0.001		0.23
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	

				Childhood Respiratory Outcomes			
	Total N[1]	**% with maternal anemia in pregnancy**	**P-value**	**% Recurrent wheeze year 1**	**P-value**	**% active asthma at age 6**	**P-value**
Household smoking – yr 1			0.19		0.34		0.75
No	566	11.5		21.7		17.1	
Yes	31	19.4		29.0		19.4	
Household smoking – yr 5			0.28		0.53		0.32
No	563	11.5		21.8		16.9	
Yes	34	17.6		26.5		23.5	
Day care – yr 1			0.63		0.002		0.88
No	400	11.5		18.4		17.5	
Yes	194	12.9		29.5		17.0	
Pets in home – yr 1			<0.0001		0.45		0.01
No	264	17.8		23.5		21.6	
Yes	333	7.2		20.9		13.8	
Pets in home – yr 5			<0.0001		0.54		0.01
No	225	18.7		23.4		22.2	
Yes	372	7.8		21.3		14.2	
Mold in home - year 1			0.65		0.74		0.66
No	506	11.7		21.9		17.0	
Yes	90	13.3		23.5		18.9	
Mold in home – yr 5			0.82		0.03		0.34
No	473	12.1		20.1		16.5	
Yes	124	11.3		29.5		20.2	

[1] Ns may not sum to total due to missing values

Table 2

Unadjusted associations between maternal anemia and childhood respiratory outcomes

		Maternal anemia[1]			
OUTCOME	**N**	**No**	**Yes**	**OR**	**95% CI**
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**

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

Ann Allergy Asthma Immunol. Author manuscript; available in PMC 2012 February 1.

Table 3

Adjusted[1] odds ratios of associations between maternal anemia and respiratory health outcomes, all children combined and stratified by maternal asthma status

OUTCOME	All children		Non-asthmatic 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**

[1]Adjusted for child's gender, 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.

Table 4

Adjusted associations between maternal anemia and childhood wheeze patterns, all children combined and by maternal asthma status[1]

Wheeze Pattern[2]	All children		Non-asthmatic 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[3]	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**

[1] Adjusted for child's gender, 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.

[2] 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

[3] NAC (not able to calculate)