



Letter

Maternal hemoglobin levels during pregnancy and asthma in childhood: the Generation R Study

Lung development and immune system maturation occur during fetal and early postnatal life.¹ The ability of the mother to provide nutrients and oxygen to the fetus is a critical factor for fetal health and development.^{1,2} Both low and high maternal hemoglobin levels have been suggested to lead to suboptimal fetal oxygen and nutrient supply and subsequent intrauterine growth restriction, which may adversely affect lung development and therefore lung function and respiratory health.^{1–3} Several studies examined the association between maternal hemoglobin levels during pregnancy and adverse birth outcomes.^{2,4} However, only a recent study by Triche et al⁵ examined the association with respiratory outcomes and found maternal anemia to be associated with an increased risk of asthma in the offspring. The aim of this study was to examine these latter findings in another longitudinal birth cohort.

This study was embedded in the Generation R study, a population-based, prospective birth cohort study.⁶ In total, 8,879 mothers with a delivery date from April 2002 through January 2006 were enrolled during pregnancy. The study was approved by the medical ethical review board of the Erasmus Medical Center, Rotterdam, the Netherlands.

Hemoglobin concentrations were measured in venous blood at enrollment (mean [SD], 14.9 [3.9] weeks) (Stichting Trombosedienst & Artsenlaboratorium Rijnmond-Medisch Diagnostisch Centrum, Rotterdam, the Netherlands).⁶ Hemoglobin concentrations were categorized as low, normal, or high (cutoffs for hemoglobin: <11 g/dL [<6.83 mmol/L]⁷ and ≥ 13.2 g/dL [≥ 8.20 mmol/L]).

Data on wheezing were obtained by parent-reported questionnaires at ages 1 to 4 and 6 years.⁸ Data on physician-diagnosed asthma ever was obtained by parent-reported questionnaires at the age of 6 years. Fractional exhaled nitric oxide (FeNO), a biomarker of eosinophilic airway inflammation, was measured using the NIOX chemiluminescence analyzer (Aerocrine AB, Solna, Sweden) at the age of 6 years. Lung function (interrupter resistance [Rint]; MicroRint, Micromedical, Rochester, Kent, England) was measured during tidal breathing, with occlusion of the airway at tidal peak expiratory flow.⁸

Potential confounders, such as sex, gestational age, birth weight, mode of delivery, and maternal complications during pregnancy, were obtained from obstetric records assessed in midwife practices and hospital registries.⁶ Data on other sociodemographic and

lifestyle factors were obtained by a combination of prenatal and postnatal questionnaires completed by both parents. These data included information on maternal age, maternal ethnicity, maternal educational level, household income per month, maternal body mass index before pregnancy, folic acid intake during pregnancy, any maternal smoking during pregnancy, multiparity, and parental history of asthma or atopy. Postnatal questionnaires included information on breastfeeding, history of cow's milk allergy, vitamin D supplementation, and day-care attendance.

Mothers without information on either hemoglobin or hematocrit levels in the first 32 weeks of pregnancy ($n = 1,280$), pregnancies leading to induced abortion ($n = 26$), fetal deaths ($n = 65$), twin pregnancies ($n = 156$) and loss to follow-up during pregnancy ($n = 38$) were excluded from the analysis. Children whose parents did not provide informed consent for school age follow-up ($n = 1,085$) were also excluded. In total, 6,229 children were available for statistical analyses.

Logistic and linear regression analyses were performed with wheezing, physician-diagnosed asthma ever, FeNO, and Rint measurements as dependent variables. Analysis were performed with FeNO as both the continuous and dichotomous variable (cutoff, 25 ppb).⁹ Maternal hemoglobin levels during pregnancy were analyzed categorically as independent variables and adjusted for gestational age at enrollment and for potential confounders based on an alteration of 10% or greater in odds ratios (ORs). To prevent attrition bias, missing values of the covariates and outcomes were multiple imputed. $P < .05$ was considered statistically significant. Statistical analyses were performed by using IBM SPSS statistical software for Windows, version 20.0 (SPSS Inc, Chicago, Illinois).

Hemoglobin levels during pregnancy were not significantly associated with wheezing at 1 to 4 years of age (data not shown). Low hemoglobin level during pregnancy was significantly associated with physician-diagnosed asthma ever (OR= 1.33; 95% CI, 1.05–1.69) (Table 1). However, this association did not remain significant after adjustment for confounders. Hemoglobin levels during pregnancy were not significantly associated with wheezing, Rint, or FeNO (continuous and dichotomous) at 6 years of age. The association between maternal hemoglobin levels and asthma-related outcomes were not significantly different by parental history of asthma or atopy ($P_{\text{interaction}} > .37$), gestational age at birth ($P_{\text{interaction}} > .27$), or birth weight ($P_{\text{interaction}} > .47$).

This study did not confirm the association between maternal hemoglobin levels during pregnancy and wheezing in early childhood or asthma outcomes at the age of 6 years. The results did not differ by paternal history of asthma or atopy, gestational age at birth, and birth weight.

Only one previous study examined the association between maternal anemia and asthma in childhood. Triche et al⁵ also found

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Table 1
Association Between Maternal Hemoglobin Levels and Asthma Outcomes at 6 Years of Age

Hemoglobin level	No. (%) of patients (N = 6,229)	Adjusted OR (95% CI) ^a	
		Crude model ^b	Multivariate model ^c
		Wheezing	
Normal	4,509 (72)	Reference	Reference
Low	810 (13)	1.28 (0.98 to 1.68)	1.18 (0.89 to 1.59)
High	909 (15)	1.01 (0.79 to 1.30)	1.06 (0.82 to 1.36)
		Physician-Diagnosed Asthma Ever	
Normal	4,509 (72)	Reference	Reference
Low	810 (13)	1.33 (1.05 to 1.69)	1.17 (0.91 to 1.50)
High	909 (15)	0.96 (0.70 to 1.32)	1.04 (0.74 to 1.46)
		FeNO ≥ 25 ppb ^d	
Normal	4,509 (72)	Reference	Reference
Low	810 (13)	1.18 (0.75 to 1.87)	1.01 (0.64 to 1.60)
High	909 (15)	0.98 (0.62 to 1.56)	1.10 (0.67 to 1.81)
		FeNO ^d	
Normal	4,509 (72)	Reference	Reference
Low	810 (13)	1.05 (0.99 to 1.12)	1.03 (0.97 to 1.10)
High	909 (15)	1.02 (0.96 to 1.08)	1.03 (0.97 to 1.10)
		Rint	
Normal	4,509 (72)	Reference	Reference
Low	810 (13)	0.01 (−0.40 to 0.42)	0.06 (−0.37 to 0.48)
High	909 (15)	0.15 (−0.15 to 0.45)	0.11 (−0.20 to 0.41)

Abbreviations: FeNO, fractional exhaled nitric oxide; OR, odds ratio; Rint, interrupter resistance.

^aORs are compared with normal hemoglobin levels during pregnancy. All values are adjusted ORs except for FeNO, which is EXP(β) (ratio of geometric means), and Rint, which is β (regression coefficient indicating the change in standardized z score compared with the reference group).

^bAdjusted for gestational age at blood sampling.

^cAdjusted for gestational age at blood sampling, maternal age, maternal ethnicity, maternal educational level, household income per month, maternal body mass index before pregnancy, parental history of asthma or atopy, sex of child, smoking during pregnancy, folic acid intake, maternal complications during pregnancy, caesarean section, birth weight z score, breastfeeding, multiparity, history of cow's milk allergy first year, vitamin D supplementation at the age of 6 to 12 months, and day-care attendance in the first 2 years of life.

^dAdditionally adjusted for FeNO technique.

maternal anemia during pregnancy not to be associated with maternal report of physician-diagnosed asthma in the child at 6 years of age. However, maternal anemia was associated with asthma outcomes at 6 years of age among children of asthmatic mothers only.⁵ This was not the case in the present study, which might be explained by the different population in the study by Triche et al, with an overrepresentation of asthmatic mothers. The latter study⁵ also found maternal anemia during pregnancy to be associated with wheeze before 3 years of age in all children, unlike in our study. It may be argued that the association between maternal anemia and childhood asthma is explained by residual confounding because we additionally adjusted our results for history of food allergy and vitamin D supplementation in infancy that may explain part of the discrepancy between the studies. Furthermore, we additionally used FeNO and Rint as objective tools to support the diagnosis of asthma and found no association.¹⁰

An important strength of this study is the large study population drawn from the general population and the wide range of potential confounders that have been taken into account. A limitation is that the information on wheezing and asthma diagnosis was obtained

by parent-reported questionnaires. This could have led to misclassification of the outcome because physician diagnosis provides more accurate outcome diagnosis. However, only when misclassification was also related to hemoglobin levels would it have influenced our results, and this is unlikely.

In conclusion, this study did not confirm the association between maternal hemoglobin levels during pregnancy and wheezing in early childhood or asthma outcomes at the age of 6 years.

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