

Letter to the Editor

Predictors of neonatal production of IFN- γ and relation to later wheeze

To the Editor:

We have shown that IFN- γ production at 3 and 9 months is inversely associated with frequent wheeze in the first year of life¹ and with wheeze up to age 13 years,² respectively. If early-life IFN- γ production predicts later wheeze, it is important to consider whether there are prenatal predictors of IFN- γ and, if so, whether these factors might actually be the driving force for the relation with wheeze. For example, if parental smoking is associated with early IFN- γ production, an observed relation between IFN- γ production and wheeze could be attributable to passive smoke exposure. In addition, there appear to be sex-specific differences in both immune responses³ and prevalence of wheeze,⁴ suggesting that potential modifications of the IFN- γ -wheeze relation by sex should be investigated. Thus the objective of this study was to investigate the predictors of cord blood IFN- γ levels, to assess whether the relation of cord blood IFN- γ levels to early wheeze is actually attributable to these factors, and to determine whether sex affects these relations.

We used data from the Infant Immune Study, a birth cohort of nonselected children.¹ Participants were healthy children born to pregnant women who planned to obtain care for their newborns from collaborating pediatricians. Blood specimens were obtained from the umbilical cord at birth and by means of venipuncture at 3 and 12 months. IFN- γ production was measured in supernatants from concanavalin A/phorbol 12-myristate 13-acetate-stimulated cord and peripheral blood mononuclear cells with ELISA, as previously described.⁵ IFN- γ levels were log transformed for all analyses. Data on maternal and paternal asthma, maternal education, household smoking during pregnancy (defined as the presence of any person who smokes in the home), ethnicity,

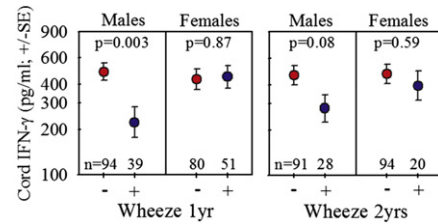


FIG 1. Relation of IFN- γ levels at birth to active wheeze at 1 and 2 years stratified by sex.

maternal age, number of children in the household, and the presence of cats or dogs in the house were obtained by questionnaire before the child's birth. Child's sex, type of delivery, gestational age, and child's birth weight were ascertained soon after delivery. Wheeze was defined as a report of wheeze in the past 12 months based on parent-completed questionnaires at age 1 (1.1 ± 0.1 years, $n = 265$), 2 (2.1 ± 0.2 years, $n = 233$), 3 (3.2 ± 0.3 years, $n = 237$), and 5 (5.1 ± 0.4 years, $n = 241$) years.

Relations between log-transformed IFN- γ levels and predictors were assessed by using t tests and linear regression models. Relations of IFN- γ to wheeze were assessed by means of logistic regression models and by using generalized estimating equations. Statistical significance for all analyses was defined by a 2-sided α level of .05. All analyses were conducted by using STATA version 10.0 software (StataCorp, College Station, Tex). The study was approved by the University of Arizona's Institutional Review Board.

Children with both IFN- γ data at birth and wheeze data at 1, 2, 3, or 5 years were included in this analysis. Included children ($n = 277$) did not differ from those not included ($n = 205$) with respect to most potential confounders. However, included children were

TABLE I. Geometric means and 95% CIs for IFN- γ production at birth by prenatal predictors and sex

	Birth IFN- γ levels (pg/mL)					
	All		Boys		Girls	
	No.*	Geometric mean (95% CI)	No.	Geometric mean (95% CI)	No.	Geometric mean (95% CI)
All	277	429 (364 to 504)	140	399 (318 to 502)	137	461 (365 to 581)
Maternal asthma						
No	215	477 (399 to 570)	115	428 (333 to 550)	100	541 (419 to 698)
Yes	52	241 (164 to 354)	21	243 (124 to 477)	33	239 (146 to 392)
P value†		.001		.09		.002
Household smoking						
No	222	474 (395 to 568)	109	447 (344 to 581)	113	502 (388 to 648)
Yes	52	295 (205 to 424)	30	271 (166 to 442)	22	332 (186 to 594)
P value†		.02		.08		.20
Other children in household						
No	128	503 (407 to 622)	61	563 (434 to 730)	67	454 (326 to 633)
Yes	137	343 (268 to 441)	72	281 (194 to 407)	65	430 (309 to 599)
P value†		.02		.004		.82
Gestational age						
Coefficient (95% CI)‡	277	-0.09 (-0.13 to -0.03)	140	-0.06 (-0.13 to 0.02)	137	-0.14 (-0.24 to -0.05)
P value‡		.004		.15		.003

Boldfacing indicates P values of less than .05.

*Total numbers vary because data on some subjects are missing for some factors.

† P value obtained from 2-sample t test with log-transformed IFN- γ levels.

‡From a linear regression model, the coefficient represents a change in log-transformed birth IFN- γ levels for a 1-week increase in gestational age.

TABLE II. ORs for the relation of birth levels of IFN- γ to active wheeze at 1 and 2 years from longitudinal models for all children stratified by sex

	All (n = 272)		Boys (n = 137)		Girls (n = 135)		Sex-IFN- γ interaction
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	P value
Unadjusted	0.6 (0.5-0.9)	.01	0.4 (0.3-0.7)	.002	0.9 (0.6-1.5)	.74	.04
Adjusted*	0.8 (0.5-1.2)	.21	0.5 (0.3-0.9)	.02	1.4 (0.8-2.4)	.24	.04

Boldfacing indicates *P* values of less than .05.

OR, Odds ratio.

*Adjusted for maternal asthma, household smoking, gestational age, and the presence of other children in the household.

more likely to have older mothers with more years of education and to live in nonsmoking households (data not shown). Table I shows geometric mean IFN- γ levels overall and with respect to selected prenatal predictors. Maternal asthma, household smoking during pregnancy, the presence of other children in the household, and gestational age were inversely related to IFN- γ production at birth. For most predictors, these relations were evident for both sexes, although they were not always statistically significant. The presence of other children in the household was only inversely associated with IFN- γ production in boys ($P_{\text{interaction}} = .054$). There was no statistically significant association between cord blood IFN- γ production and sex, type of delivery, maternal age at delivery, maternal education, paternal asthma, ethnicity, presence of cats or dogs in the house, or child's birth weight (data not shown).

Of the 277 subjects included in this analysis, 92.4% ($n = 256$) had data on both early wheeze (at either 1 or 2 years) and later wheeze (at either 3 or 5 years). The prevalence of active wheeze was 34.1% (90/264), 20.6% (48/233), 22.8% (54/237), and 24.9% (60/241) at age 1, 2, 3, and 5 years, respectively. Active wheeze prevalence was not significantly associated with sex at any age.

Fig 1 shows the geometric mean production of cord blood IFN- γ by active wheeze at 1 and 2 years stratified by sex. Boys who were wheezing in the first 2 years of life had lower IFN- γ production at birth than nonwheezers, a relation that did not exist for girls. Predictive relations of IFN- γ with wheeze to 2 years are shown in Table II. For the group as a whole, cord blood IFN- γ levels were inversely associated with wheeze through age 2 years, although this relation was not statistically significant after adjustment for maternal asthma, household smoking, gestational age, and other children in the household. When stratified by sex, cord blood IFN- γ levels were inversely associated with wheeze for boys through age 2 years in both unadjusted and adjusted models. There was no relation of cord blood IFN- γ levels with wheeze to 2 years for girls ($P_{\text{interaction}} = .04$). IFN- γ production at 3 months was also inversely associated with wheeze through age 2 years, and again, this relation was primarily seen for boys (see Table E1 in this article's Online Repository at www.jacionline.org). There was no association between IFN- γ production at 12 months and wheeze through age 2 years (see Table E1). There was no association between IFN- γ production at birth, 3 months, or 12 months with wheezing at ages 3 or 5 years either overall or when stratified by sex (data not shown). Relations between IFN- γ production and wheeze were similar for infants

who were atopic or nonatopic, as indicated by detectable allergen-specific IgE by age 2 years (data not shown).

Our results expand on those of Guerra et al¹ by using a larger dataset from the same population and by adjusting for prenatal predictors of cord blood IFN- γ . Whereas Guerra et al¹ found no overall association between cord blood IFN- γ and wheeze, in the current analysis stratification by sex revealed an association among boys that persisted after adjustment for potential confounders.

In conclusion, this analysis reveals a relation of IFN- γ production at birth to wheeze that is only evident for boys and is limited to the first 2 years of life. Furthermore, predictors of IFN- γ production at birth do not account for these relations. These findings reinforce the importance of considering sex when evaluating the relation between risk factors and disease.

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TABLE E1. ORs for the relation of 3-month and 12-month IFN- γ levels to active wheeze at 1 and 2 years from longitudinal models for all children stratified by sex

IFN- γ	All (n = 272)		Boys (n = 137)		Girls (n = 135)		Sex-IFN- γ interaction
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	<i>P</i> value
3 mo	0.6 (0.3-1.0)	.07	0.4 (0.2-0.9)	.03	0.9 (0.4-2.2)	.87	.17
12 mo	0.9 (0.6-1.3)	.45	0.9 (0.5-1.5)	.64	0.9 (0.5-1.4)	.54	.94

Boldfacing indicates *P* values of less than .05.

OR, Odds ratio.