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Fetal umbilical, cerebral and pulmonary blood flow patterns in relation to lung function and asthma in childhood. The Generation R Study

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Abstract

Background: Fetal growth restriction is associated with higher risks of childhood respiratory morbidity. Fetal blood flow adaptations might contribute to these associations. We examined the associations of fetal umbilical, cerebral, and pulmonary blood flow with wheezing patterns, lung function, and asthma in childhood.

Methods: In a population-based prospective cohort study among 903 children, we measured fetal umbilical, cerebral, and pulmonary blood flow by pulsed-wave Doppler at a median gestational age of 30.3 (95% range 28.8-32.3) weeks. We obtained information about wheezing patterns until the age of 6 years by questionnaires. Lung function was measured by spirometry and information about current asthma was obtained by questionnaire at the age of 10 years.

Results: Results showed a non-significant relationship between a higher umbilical artery pulsatility index (PI) and umbilical artery PI/cerebral artery PI ratio, indicating fetal blood flow redistribution at the expense of the trunk, with higher risks of early wheezing (OR [95% CI]: 2.07 (0.70-6.10) and 2.74 (0.60, 12.62) per unit increase, respectively). A higher pulmonary artery time velocity integral, indicating higher pulmonary vascular resistance, was associated with a higher risk of late/persistent wheezing (Z-score 1.14 [1.01-1.29]). A higher middle cerebral artery PI was associated with a higher FEV_1/FVC (Z-score [95% CI]: 0.21 [0.01-0.42]). Results did not materially change after additional adjustment for birth and growth characteristics.

Conclusion: Third-trimester fetal blood flow patterns might be related to childhood respiratory health. These findings should be considered as hypothesis generating and need further replication.

KEYWORDS
asthma, epidemiology, fetal blood flow, lung function, wheezing

1 | INTRODUCTION

Pregnancy is a critical period for fetal lung development. In late fetal life, the small airways and alveoli are formed.[1] An adverse intrauterine environment in this period seems to have persistent effects on respiratory health and disease across the life course.[2] Fetal blood flow adaptations are important mechanisms by which the fetus protects the most important organs such as the brain and heart from an adverse fetal environment.[3] A preferential fetal blood flow to the brain at the expense of the trunk is characterized by changes in fetal blood flow including a higher umbilical and lower cerebral arterial resistance.[4,5] This redistribution of fetal blood flow may be beneficial for short-term survival but may lead to a lower delivery of oxygen and nutrients to the trunk, including the lungs and airways.[6,7] A potential consequence of fetal blood flow redistribution is a reduction in number and metabolism of alveolar type II cells, fewer but larger alveoli, and impaired growth and maturation of the airways and lungs.[8,9] Impaired fetal development of the airways and lungs could predispose individuals to a higher risk of lung disease in later life.[8] Previous studies reported associations of fetal growth restriction with impaired lung function and respiratory diseases in later life.[10,11] We previously showed that fetal growth restriction and being born small for gestational age were associated with higher airway resistance and lower lung function in childhood.[12] Fetal blood flow adaptations related to fetal growth restriction may underlie these associations. Although the effects of fetal umbilical and cerebral blood flow adaptations on fetal and childhood growth are well known, it is unknown whether fetal blood flow adaptations affect childhood respiratory morbidity. Also, the role of a suboptimal fetal pulmonary blood flow on the development of respiratory morbidity is unclear.

Therefore, we examined in a population-based prospective cohort study among 903 children the associations of fetal umbilical, cerebral, and pulmonary blood flow with wheezing at age 6 years, and lung function and asthma in children aged 10 years. We also explored whether birthweight, gestational age at birth, or childhood growth mediated these associations.

Key Message

An adverse intrauterine environment may have consequences on respiratory health and disease across the life course. We assessed whether fetal blood flow adaptations are related to lung function development and asthma risk in childhood. Non-significant tendencies towards associations for fetal blood flow redistribution with higher risk of early wheezing were found, a higher pulmonary vascular resistance was associated with higher risk of late/persistent wheezing. This study is the first that examines these associations. Our findings are important from an etiological and developmental perspective, providing evidence that changes in fetal blood patterns may lead to altered respiratory health.

2 | METHODS

2.1 | Design and study population

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward in Rotterdam, the Netherlands.[13] The Medical Ethics Committee of the Erasmus MC, University Medical Center, Rotterdam, has approved the study. Written informed consent was obtained from all participants. Detailed assessments of fetal growth and development were conducted in a random subgroup of 1232 Dutch mothers and children born between April 2002 and January 2006.[4] The present analyses were performed on 903 children (Figure 1).

2.2 | Third-trimester fetal blood flow

Fetal blood flow measures were assessed by pulsed-wave Doppler at a median gestational age of 30.3 (95% range 28.8-32.3) weeks.

Feto-placental vascular resistance was evaluated with recorded flow-velocity waveforms from the umbilical artery. Umbilical artery pulsatility index (PI) was determined in a free-floating loop of the umbilical cord. A higher umbilical artery PI indicates a higher peripheral vascular resistance.[14] Middle cerebral artery Doppler measurements were performed with visualization of the circle of Willis in the fetal brain, and flow-velocity waveforms were obtained in the proximal part of the cerebral arteries. The middle cerebral artery PI quantifies the redistribution of blood flow, and when lower, in favor of the fetal brain. Reductions in middle cerebral artery PI are valid indicators of the brain-sparing effect and fetal redistribution.[15] An indicator of the "brain-sparing effect" is a raised ratio between the umbilical artery PI and the cerebral artery PI (U/C ratio).[5].

Pulmonary outflow flow-velocity waveforms from the aorta were recorded from the five-chamber view and the short-axis view of the fetal heart just above the semilunar valves. Time velocity integral (TVI) during systole was recorded. A higher pulmonary artery TVI indicated higher pulmonary vascular resistance.[16].

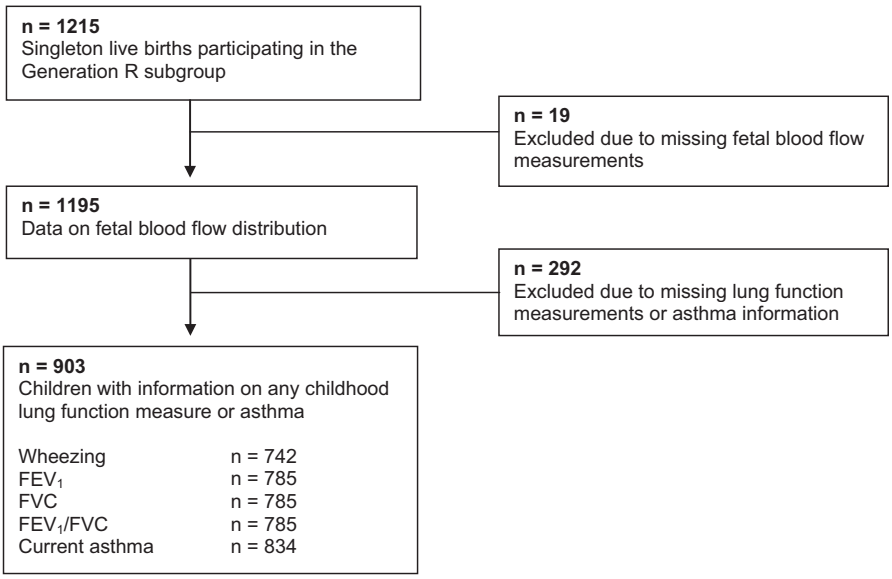

FIGURE 1 Flowchart of participants included in the analysis

Reproducibility of ultrasound measurements was adequate with high intraclass correlation coefficient values (>0.80) with corresponding low variation coefficient values (<10%).[4] All ultrasound examinations were performed with an ATL-Philips model HDI 5000 (Seattle, Washington, USA) equipped with a 5.0-MHz high-frequency, curved-array transducer.

2.3 | Childhood lung function and asthma

Information about wheezing was obtained by questionnaires until 6 years. We constructed wheezing patterns based on time of onset and subsequent absence or persistence ("never"; "early" [≤3 years only]; "late" [>3-6 years] and "persistent wheezing") in children with information on wheezing for at least two time points.[17] Children visited the research center at a median age of 9.7 years (range 8.5-12.0 years), and we performed spirometry: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. Spirometry was performed according to the American Thoracic Society and European Respiratory Society recommendations.[18] All spirometry variables were converted into sex-, age-, height-, and ethnicity-adjusted z-scores.[19] Current asthma (no; yes) was defined as physician-diagnosed asthma ever, with either wheezing or the use of (airway) medication in the past 12 months by questionnaires at age 10 years.

2.4 | Covariates

We obtained information on maternal educational level, pre-pregnancy weight, parity, smoking during pregnancy, folic acid use during pregnancy, and history of asthma or atopy, from questionnaires. Maternal height was measured and pre-pregnancy BMI was calculated (kg/m^2). Estimated fetal weight in the third trimester was calculated.[20] Information on gestational hypertensive disorders, child's sex, gestational age at birth, and birthweight was obtained by midwife and hospital registries. At age 10 years, information on ever diagnosis of eczema was obtained by questionnaire. During the research center visit at age 10 years, child height and weight were measured using Standard Operating Procedures. We measured the children without shoes and heavy clothing, and BMI was calculated. Allergic sensitization to the most common inhalant allergens (house dust mite, grass, birch, cat, and dog; ALK-Abelló BV, Almere, The Netherlands) was determined by a skin prick test using the "scanned-area method."[21].

2.5 | Statistical analysis

First, we performed a non-response analysis by assessing the differences in characteristics of participants included and not included in the study. Second, we assessed the associations of fetal blood flow with wheezing patterns, lung function, and asthma using multivariate logistic or linear regression models. These models were first adjusted for gestational age at third-trimester fetal blood flow measurement and estimated fetal weight at third-trimester fetal blood flow measurement or child sex only (basic model), and secondly, additionally adjusted for maternal educational level, pre-pregnancy BMI, parity, smoking, folic acid use, and gestational hypertensive disorders (adjusted model). We used generalized estimating equations (GEEs) to examine longitudinal effects of fetal blood flow with the risk of overall wheezing until age 6 years. These models take into account the correlations between repeated measurements within the same subject. An unstructured correlation matrix was used. Third, we examined whether any association of fetal blood flow with wheezing patterns, lung function, or asthma was mediated by birthweight or gestational age at birth or child's BMI at age 10 years by adding them additionally in our models (mediation model). Furthermore, we examined whether maternal history of asthma or atopy, child's eczema, or inhalant allergic sensitization modified any association by analyzing the statistical interaction between these variables and the fetal blood flow–related exposures (effect modification

model). The percentages of missing covariate values within the population for analysis were lower than 19%. Missing covariate data were imputed using the multiple imputations procedure (n = 5 imputations), and the imputed datasets were analyzed together. All measures of associations are presented with their 95% confidence intervals (CI). Statistical analyses were performed using SPSS version 24.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

3 | RESULTS

3.1 | Participant characteristics

Table 1 shows the characteristics of the mothers and children included in the current study. Table S1 shows the participant characteristics before multiple imputation. Non-response analyses showed that mothers of children not included in the analysis were more frequently lower educated, had a higher prevalence of multiparity, smoked more often, and used less often folium acid supplement during pregnancy. Their children were born at a younger gestational age (Table S2).

3.2 | Fetal blood flow and wheezing patterns until age 6 years

Table 2 shows, in the adjusted models, a non-significant relationship between a higher umbilical artery PI with higher risks for early and late/persistent wheezing in children (odds ratio [OR] 2.07 [95% CI, 0.70, 6.10] and 1.68 [0.34, 6.50] per unit increase in umbilical artery PI, respectively). Similarly, a higher U/C ratio, which indicates redistribution of blood flow in favor of the fetal brain, tended to be associated with a higher risk for early wheezing (OR, 2.74 [0.60, 12.62] per unit increase in U/C ratio). None of these associations were statistically significant. Middle cerebral artery PI was not associated with wheezing patterns. A higher pulmonary artery TVI, which indicates higher pulmonary vascular resistance, was associated with a higher risk of late or persistent wheezing (OR, 1.14 [1.01, 1.29] per unit increase in pulmonary artery TVI). The effect estimates for the associations of fetal umbilical, cerebral, and pulmonary blood flow adaptations with wheezing patterns adjusted for gestational age at third trimester, estimated fetal weight, and child sex only (basic model) were similar as for the adjusted models, and are presented in Table S3.

3.3 | Fetal blood flow and lung function and asthma at age 10 years

Table 3 shows that in the adjusted models, a higher third-trimester fetal middle cerebral artery PI was associated with a higher FEV_1/FVC only (Z-score, 0.21 [95% CI, 0.01, 0.42] per unit increase middle cerebral artery PI). We observed no consistent associations of fetal blood flow with other lung function measures. Results from the models focused on these associations adjusted for gestational age at third trimester, estimated fetal weight, and child's sex only

TABLE 1 Characteristics of children and their mothers after multiple imputation (n = 903)

	Study population
Maternal characteristics	
Education (%)	
Low (no, primary, secondary education)	32.9 (297)
High (higher education)	67.1 (606)
Pre-pregnancy body mass index (kg/m^2)	23.6 (3.9)
Parity (%)	
Nullipara	62.8 (567)
Multipara	37.2 (336)
History of asthma or atopy (%)	
No	61.7 (557)
Yes	38.2 (346)
Smoking during pregnancy (%)	
No smoking throughout pregnancy	79.1 (714)
Yes	20.9 (189)
Folic acid supplement use (%)	
No use	8.2 (74)
Start within the first 10 wk of pregnancy	29.3 (265)
Preconceptional start	62.5 (564)
Pregnancy-induced complications (gestational hypertension/preeclampsia) (%)	
No	91.7 (828)
Yes	8.3 (75)
Third-trimester fetal characteristics	
Gestational age at measurement, wk	30.4 (28.5-32.7)
Estimated fetal weight, grams	1632 (266)
Umbilical artery PI	0.97 (0.16)
Middle cerebral artery PI	1.97 (0.33)
Umbilical/middle cerebral artery ratio	0.50 (0.11)
Pulmonary artery time velocity integral	12.04 (1.83)
Birth characteristics	
Gestational age at birth, wk	40.3 (36.7-42.4)
Birthweight, g	3528 (509)
Sex	
Male	50.6 (457)
Female	49.4 (446)
Childhood characteristics	
Wheezing patterns until 6 y (%)	
Never	45.8 (414)
Early	23.0 (208)

(Continues)

TABLE 1 (Continued)

	Study population
Late/persistent	13.3 (120)
Missing	17.8 (161)
Age at follow-up, y	9.8 (9.1-10.5)
Body mass index at age 10 y (kg/m^2)	17.1 (2.2)
Ever eczema at age 10 y (%)	
No	73.9 (667)
Yes	26.1 (236)
Inhalant allergic sensitization at age 10 y (%)	
No	67.7 (611)
Yes	32.3 (292)
Current asthma (%)	
No	88.7 (801)
Yes	3.7 (33)
Missing	7.6 (69)
FEV_1 (L/s)	2.05 (0.29)
FVC (L)	2.39 (0.35)
FEV_1/FVC	0.86 (0.06)

Values are means (standard deviation), medians (95% range), or valid percentages (absolute numbers). Data were not imputed for the third trimester, birth characteristics, and respiratory outcomes. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NI, not imputed; PI, pulsatility index.

(basic model) showed no associations of fetal umbilical, cerebral, and pulmonary blood flow with lung function or asthma at age 10 years (Table S4).

Results of the associations of fetal umbilical, cerebral, and pulmonary blood flow with wheezing patterns, lung function, or asthma did not materially change after adding the mediators birthweight, gestational age at birth, or BMI at age 10 years (mediation model, data not shown). The associations were not modified by maternal history of asthma or atopy or child's eczema or inhalant allergic sensitization (effect modification model, all *P*-values for interaction >0.05).

4 | DISCUSSION

We observed a non-significant relationship between a higher umbilical artery PI and U/C ratio with higher risk of early and late/persistent wheezing. A higher pulmonary artery TVI was associated with a higher risk of late/persistent wheezing. We found that a higher middle cerebral artery PI was associated with a higher FEV_1/FVC. Associations were not explained by birth parameters, current BMI, or allergic predisposition. No other consistent associations of changes in fetal umbilical, cerebral, or pulmonary blood flow with wheezing patterns until age 6 years, or lung function and asthma at age 10 years, were found.

4.1 | Interpretation and comparison with previous studies

An adverse intrauterine environment in the developing fetus leads to fetal blood flow adaptations. These adaptations may be beneficial for short-term survival but may lead to a lower delivery of oxygen and nutrients to the trunk.[6] Fetal blood flow adaptations can be detected by umbilical vein blood flow. A compensatory increase in ductus venous diameter increases the blood flow to the heart.[22] This is eventually followed by a higher umbilical artery blood flow resistance and a decrease in cerebral artery resistance.[23] Subsequently, changes in the pulmonary arteries can be observed, such as a higher pulmonary TVI.[24] For the current study, we hypothesized that fetal umbilical, cerebral, and pulmonary blood flow adaptations may affect growth and maturation of the airways and lungs, which predispose individuals to lung disease.[8,9]

Fetal blood flow adaptations are related to fetal growth restriction or low birthweight with further consequences for childhood

TABLE 2 Associations of third-trimester fetal blood flow with wheezing patterns until the age of 6 y (adjusted model)

	Never wheezing Odds ratio (95% CI) (n = 414)	Early wheezing Odds ratio (95% CI) (n = 208)	Late or persistent wheezing Odds ratio (95% CI) (n = 120)	Overall wheezing Odds ratio (95% CI) (n = 386)
Umbilical artery PI (n = 884)	Reference	2.07 (0.70, 6.10)	1.68 (0.34, 6.50)	1.61 (0.92, 2,83)
Middle cerebral artery PI (n = 877)	Reference	0.77 (0.46, 1.31)	1.08 (0.56, 2.05)	1.06 (0.81, 1.39)
Umbilical/middle cerebral artery ratio (n = 858)	Reference	2.74 (0.60, 12.62)	0.96 (0.14, 6.80)	1.07 (0.48, 2.41)
Pulmonary artery time velocity integral (n = 788)	Reference	1.01 (0.91, 1.12)	1.14 (1.01, 1.29)*	1.03 (0.98, 1.08)

Values are odds ratios (95% confidence intervals) from logistic regression models and generalized estimating equation models (overall wheezing; wheezing on at least one time point). "n" represents number of cases. Models were adjusted for maternal educational level, parity, body mass index, smoking, folic acid use, pregnancy complications and gestational age at third trimester, estimated fetal weight, and child sex. PI, pulsatility index.
*$P < 0.05$.

TABLE 3 Associations of third-trimester fetal blood flow with lung function and asthma at age 10 y (adjusted model)

	FEV_1 Z-score (95% CI) (n = 785)	FVC Z-score (95% CI) (n = 785)	FEV_1/FVC Z-score (95% CI) (n = 785)	Current asthma Odds ratio (95% CI) (n = 834)
Umbilical artery PI (n = 884)	−0.06 (−0.46, 0.33)	−0.23 (−0.61, 0.14)	0.32 (−0.09, 0.74)	2.54 (0.26, 24.59)
Middle cerebral artery PI (n = 877)	0.01 (−0.18, 0.20)	−0.10 (−0.28, 0.08)	0.21 (0.01, 0.42)*	0.83 (0.28, 2.44)
Umbilical/middle cerebral artery ratio (n = 858)	−0.16 (−0.73, 0.41)	−0.20 (−0.74, 0.34)	0.09 (−0.52, 0.69)	0.84 (0.03, 23.28)
Pulmonary artery time velocity integral (n = 788)	0.01 (−0.03, 0.05)	0.02 (−0.01, 0.06)	−0.04 (−0.08, 0.01)	1.08 (0.88, 1.34)

Values are z-score differences or odds ratios (95% confidence intervals) and reflect the change in lung function or risk for asthma per change in fetal blood flow. Lung function variables were converted into sex-, height-, age-, and ethnicity-adjusted z-scores. Models were adjusted for maternal educational level, parity, body mass index, smoking, folic acid use, pregnancy complications and gestational age at third trimester, estimated fetal weight, and child sex. $FEV_{1,}$ forced expiratory volume in 1 s; FVC, forced vital capacity; PI, pulsatility index.
*$P < 0.05$.

respiratory health.[12] Umbilical placental embolization in sheep was associated with structural alterations in the lungs, such as fewer but larger alveoli and a 10% reduction in the internal surface area.[9] Another animal study did not find differences in lung growth after umbilical placental embolization, but did find higher pulmonary deoxyribonucleic acid and plasma cortisol levels suggesting that the offspring lungs remain underdeveloped during life.[25] Children born with a very low birthweight or preterm are at higher risks of severe chronic respiratory diseases, such as bronchopulmonary dysplasia (BPD).[26] Intrauterine conditions such as abnormal placental flow or suboptimal development of the placenta may lead to an increased expression of angiogenic factors, such as soluble fms-like tyrosine kinase-1 and vascular endothelial growth factor, which increases the risk of chronic respiratory diseases in childhood.[27,28] Also, an elevated inflammation status, found in growth restricted fetuses, could lead to reduced lung function later in life.[29] Impaired vasculogenesis and angiogenesis, found in children with intrauterine growth restriction, might be other mechanisms than structural lung growth alterations leading to a suboptimal lung development.[30] Children with fetal growth restriction might be vulnerable to more adaptive processes and have increased risk of respiratory morbidity in later life. Furthermore, maternal hypertensive disorders during pregnancy could have an effect on respiratory morbidity through multiple underlying mechanisms such as a disturbed placental blood flow and an altered angiogenic status. Previously published studies have shown that hypertensive disorders in pregnancy might be related to lower lung function in newborn infants or increased risk of wheezing.[31,32] A recent study from the same cohort as the current study reported associations for blood pressure across the full range in different trimesters with asthma-related outcomes in childhood, but not for maternal hypertensive disorders with these outcomes.[34] The role of fetal blood flow patterns for these associations is not clear. Our observed associations were not mediated through birthweight or gestational age at birth, but a possible role of the placenta or inflammatory status of the newborn warrants further studies.

Our study resulted mainly in negative findings, with two exceptions. First, our results showed that an increase in TVI was related to late/persistent wheezing. An increased TVI might be a sign of underdevelopment of the fetal airways, such as fewer but larger alveoli and impaired growth of the airways and lungs.[8,9] This finding might suggest that pulmonary blood flow in fetal life might be related to an increased risk of late/persistent wheezing in later life. A higher middle cerebral artery PI was associated with a higher FEV_1/FVC. Our results showed a non-significant inverse relation of the middle cerebral artery PI with FVC, but no association was observed for FEV_1. We speculate that flow patterns related to fetal brain sparing might have consequences for the growth of the lungs. However, as no other effects of fetal blood flow measures on lung function or asthma in childhood were found, the observed association might be a chance finding.

4.2 | Strengths and limitations

The main strength of this study was the large population-based cohort examined from fetal life onward. To our knowledge, this is the first study to examine the effects of fetal blood flow on respiratory outcomes. The population-based setting enabled us to assess the fetal blood flow across the full range, rather than only in fetuses with growth restriction or other complications. Follow-up measurements at the age of 10 years were available in 74% of the children. Missing information about wheezing, lung function, or asthma could lead to selection bias and loss of power. Our results would be biased if the associations between fetal blood flow and wheezing, lung function, or asthma differed between those included and those not included in the study. Although this seems unlikely, it cannot be excluded. In the present study, we evaluated multiple associations. However, because of the correlations between the outcome measures, we did not correct for multiple testing. Our results were inconsistent and the associations might be a chance finding. In this study, there might have occurred some bias toward a more affluent and healthy population due to differences in characteristics between those lost to follow-up and included in the study.[13] Information on wheezing patterns, asthma, and eczema was obtained by questionnaires, adapted from the ISAAC-Core questionnaires. These have been validated and shown adequate for epidemiological studies.[35] However, misclassification due to under- or overreporting cannot be excluded. Finally, although

we had information about a large number of confounders, the influence of residual confounding should be considered, as in any observational study.

4.3 | Conclusion and perspectives

The results of our study are important from an etiological perspective. Our findings suggest that adaptations in fetal blood flow might contribute to the risk of wheezing and lung function in childhood. However, the observed effects were small or non-significant and may reflect subclinical changes only. These findings should be considered as hypothesis generating and need further replication.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

MK, EM, and LD contributed to the conception and design and acquisition, analyses, and interpretation of the data; drafted the article; revised it critically for important intellectual content; and gave final approval of the version to be published. ES, IR, JJ, and VJ contributed to the conception and design and acquisition of data; revised the drafted manuscript critically for important intellectual content; and gave final approval of the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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