Neonatal rhinorrhea, heart rate variability, and childhood exercise-induced wheeze

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Background: There is increasing evidence linking infant rhinorrhea to school-age exercise-induced wheeze (EIW) via a parasympathetic nervous system pathway. The ratio of the root mean square of successive differences in heart beats (RMSSD) measured in quiet sleep versus active sleep ($RMSSD_{QS:AS}$) is a novel biomarker in asthma.

Objective: We tested the hypotheses that (1) neonatal rhinorrhea predicts childhood EIW independent of other neonatal respiratory symptoms, (2) neonatal $RMSSD_{QS:AS}$ predicts childhood EIW, and (3) $RMSSD_{QS:AS}$ mediates the association between neonatal rhinorrhea and childhood EIW.

Methods: Participants from the Safe Passage/Environmental Influences on Child Health Outcomes (PASS/ECHO) prospective birth cohort had heart rate variability extracted from electrocardiogram traces acquired in the first month of life. Parents reported on rhinorrhea in their child at age 1 month and on EIW in their child at ages 4 to 11 years.

Results: In models (N = 831) adjusted for potential confounders and covariates, including neonatal wheeze, cough and fever, neonatal rhinorrhea–predicted childhood EIW (relative risk [RR] = 2.22; $P = .040$), specifically, among females (RR = 3.38; $P = .018$) but not males (RR = 1.39; $P = .61$). Among participants contributing data in both active and quiet sleep (n = 231), $RMSSD_{QS:AS}$ predicted EIW (RR = 2.36; $P = .003$) and mediated the effect estimate of neonatal rhinorrhea predicting EIW among females. Half of the females with a higher $RMSSD_{QS:AS}$ and neonatal rhinorrhea (n = 5 of 10) developed EIW as compared with 1.8% of the other females (n = 2 of 109) ($P < .001$).

Conclusions: Our findings support dysregulation of the parasympathetic nervous system in infancy as one of the possible underlying mechanisms for the development of EIW later in childhood among females, which could aid in the development of future interventions. (J Allergy Clin Immunol Global 2023;2:100149.)

Key words: *Asthma, exercise induced asthma, rhinitis, watery eyes, parasympathetic nervous system, heart rate variability and sleep states*

Although the link between rhinorrhea and asthma is thought to occur primarily through an allergic pathway, a nonallergic pathway involving an imbalance of parasympathetic nervous system (PNS) signaling may have a significant role in manifestations of rhinorrhea and asthma.[1-3] PNS signaling is involved in nasal obstruction, nasal discharge, and sneezing, and anticholinergic treatment has been shown to reduce all of these nasal symptoms.[4-7] The PNS is the dominant neuronal pathway in the control of airway smooth muscle tone, and its overstimulation can result in increased airway constriction and asthma symptoms.[1,2] The PNS is also involved in controlling heart rate. Measuring high-frequency heart rate variability (HF-HRV) offers a convenient and noninvasive biomarker for assessing PNS activity.[8-10] The root mean square of the successive differences (RMSSD) is a time domain measure of beat-to-beat variability. As such, it is thought to be modulated predominantly by PNS activity.[8,10,11]

From several cohorts in New York City (NYC) and the Northern Plains (North Dakota and South Dakota), we have findings leading to and supporting our premise that dysregulation of the autonomic nervous system (ANS) in infancy can lead to airway hyperreactivity at school age.[12] Overall, we theorize that ANS dysregulation, which can be measured by heart rate variability (HRV), manifests in infancy as rhinorrhea and/or watery eyes and leads to increased risk of airway hyperreactivity at school age, causing exercise-induced wheeze (EIW) and unscheduled medical visits for asthma (Fig 1). Among children living in NYC, report of rhinorrhea or watery eyes without a cold in infancy predicted school age EIW, emergency department visits, and hospitalizations for asthma independent of wheeze and indicators of allergic sensitization.[12] In addition, prenatal exposure to organophosphate pesticides and maternal stress, both of which can increase PNS signaling in infants,[13-15] predicted infant rhinorrhea and/or watery eyes.[16,17] Furthermore, increased HF-HRV measured in infancy was associated with rhinorrhea and/or watery eyes at the same age among children in NYC and predicted subsequent wheeze at age 2 to 3 years among children in the Northern Plains.[18,19] The latter association was observed among females but not among males.

Importantly, in both NYC and the Northern Plains studies, we have observed the strongest associations between measures of HF-HRV collected during non–resting state protocols (eg, mother-infant still-face and head-up tilt challenges).[18,19] Newborns alternate between 2 sleep stages, active sleep (AS)

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Abbreviations used

ANS: Autonomic nervous system
AS: Active sleep
ECHO: Environmental influences on Child Health Outcomes
ECG: Electrocardiogram
EIW: Exercise-induced wheeze
HF-HRV: High-frequency heart rate variability
HRV: Heart rate variability
IQR: Interquarile range
NYC: New York City
PNS: Parasympathetic nervous system
PR: Prevalence ratio
QS: Quiet sleep
RMSSD: Root mean square of successive differences in heart beat
$RMSSD_{QS:AS}$: Ratio of RMSSD in quiet sleep to RMSSD in active sleep
RR: Relative risk

and quiet sleep (QS). During AS, respiration is more rapid and irregular and heart rate is higher, with lower HF-HRV than during QS.[20,21] Cycling from AS to QS involves heart rate adjustments regulated by the PNS. Therefore, the ratio of HF-HRV in QS to HF-HRV in AS, specifically RMSSD, could indicate beat-to-beat HRV activity modulated predominantly by the PNS and serve as a relatively easy, noninvasive method for assessing PNS tone.

With this study, we aimed to demonstrate connections between infant rhinorrhea, increased PNS activity, and childhood EIW in 1 cohort to both increase the generalizability of findings seen in NYC and establish stronger evidence for these connections. We studied children in the Safe Passage Study (PASS)/Environmental Influences on Child Health Outcomes (ECHO) (PASS/ECHO) cohort in the Northern Plains, where we previously reported associations between infant HF-HRV and wheeze at age 2 to 3 years.[18] We tested the hypotheses that (1) neonatal rhinorrhea would predict childhood EIW and asthma independent of neonatal wheeze and indicators of current respiratory infection; (2) the ratio of RMSSD in QS to RMSSD in AS ($RMSSD_{QS:AS}$), as an indicator of PNS tone, would be associated with neonatal runny nose and childhood EIW and asthma; (3) $RMSSD_{QS:AS}$ would partially mediate the association between neonatal rhinorrhea and school-age EIW and asthma; (4) the combination of $RMSSD_{QS:AS}$ and infant rhinorrhea would predict school-age EIW and asthma; and (5) these associations would be observed to a greater degree among females than among males.

METHODS

Study design

The PASS/ECHO study is a prospective birth cohort initially designed to investigate the impact of prenatal exposure to alcohol, smoking, and other environmental factors on sudden infant death syndrome, stillbirth, and fetal alcohol spectrum disorders.[22] Institutional review board approvals were obtained from sponsoring organizations at the participating clinical sites in the Northern Plains, Data Coordinating Center, Physiologic Assessment Center, Columbia University, and New York Psychiatric Institute. Informed consent was obtained.

Setting and participants

The PASS cohort enrolled pregnant women between 2007 and 2015 in the Northern Plains, as described previously.[22,23] Women who were aged 16 years or older, able to provide informed consent, pregnant with 1 or 2 fetuses, and able to speak English were recruited. The exclusion criteria included planned abortion, planned move from the catchment area before delivery, and medical advice against participation in the study.[22] Under the NIH ECHO initiative, PASS participants were recontacted starting in 2017. Children were included in the analyses for this article if they had data available on respiratory symptoms at ages 1 month and 4 to 11 years.

Self-reported maternal characteristics were collected at the earliest prenatal visit. Maternal diagnoses of asthma and depression were abstracted from medical records.

Neonatal HRV

As described previously, cardiorespiratory assessments were performed in the 12 to 96 hours after birth and/or at age 1 month.[23] For infants born preterm (<37 weeks of gestation), visits were conducted at term-equivalent ages (eg, 39-41 weeks for newborns). Physiologic assessments were completed between 9 AM and 4 PM. Approximately 30 minutes after the child was fed, electrocardiogram (ECG) electrodes were placed on the infant. ECG and respiration were recorded while the child slept in the prone position during a 10-minute baseline period before head-up tilt challenge. Challenge data were not used in these analyses. Sleep stages (AS and QS) of the infants were coded retrospectively by using a breathing rate variability method described previously.[20] ECG and respiratory waveforms were preprocessed by using previously described algorithms. Epochs with a substantial number of artifacts (from line noise and/or child movement) were discarded.[23] Data were analyzed in 1-minute epochs, which were subsequently averaged by sleep states. More details and related sensitivity analyses are described in the Supplementary Material (see the Online Repository at www.jaci-global.org). For these analyses, the primary HRV variable tested was the ratio of RMSSD collected in QS to that collected in AS:

$$\mathrm{RMSSD_{QS:AS}} = \frac{RMSSD_{QS}}{RMSSD_{QA}}$$

Relative risks (RRs) for respiratory outcomes were calculated for an interquartile range (IQR) increase in $RMSSD_{QS:AS}$.

Neonatal respiratory symptoms

When their child was aged 1 month, parents were asked questions about the child's health. A child was considered to have neonatal rhinorrhea if the parent answered yes to the question, "During the last 2 weeks, has your baby had a runny nose or cold?" Cough was assessed with the question, "During the last 2 weeks, has your baby had a cough?"; wheeze was assessed with the question, "Since the baby was born, has she or he ever wheezed or made whistling noises when breathing"; and fever was assessed with the question, "Since the baby was born, has she or he ever felt feverish or hot?"

Childhood respiratory symptoms

Between ther ages 4 and 11 years, respiratory health questionnaires were administered. Questions about symptoms in the past

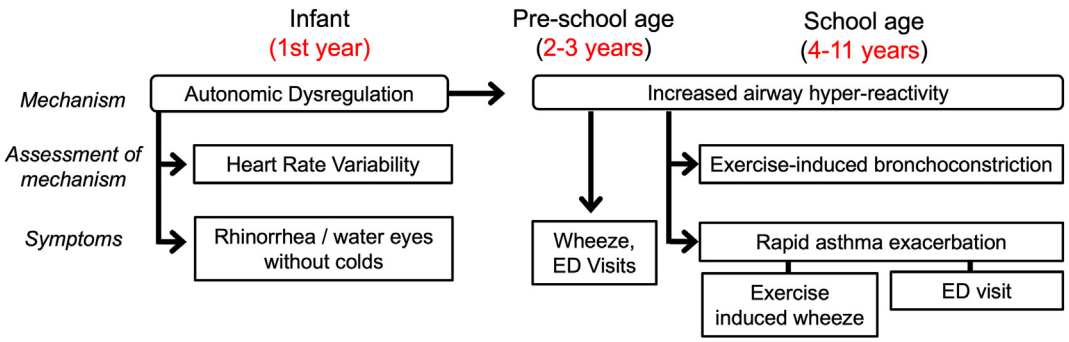

FIG 1. Proposed model of infant ANS dysregulation leading to school age airway hyperreactivity. *ED,* Emergency department.

TABLE I. Demographics of study participants at birth

Demographic characteristic	All children (N = 831)
Gestational age at birth (wk), mean (SD)	39.0 (1.8)
Maternal age at child's birth (y), mean (SD)	28.6 (4.8)
Female sex, no. (%)	422 (50.8)
Child's birth order, no. (%)*	
Firstborn	289 (34.8)
Second born	292 (35.1)
Third or later born	250 (30.1)
Child's reported race, no. (%)†	
American Indian	150 (18.1)
White	653 (78.6)
Other/not reported	28 (3.4)
Mother's health from medical record, no. (%)‡	
Asthma	127 (15.3)
Depression	101 (23.9)
Sociodemographics	
Married or partnered, no. (%)	773 (93.0)
Mother graduated from high school, no. (%)	774 (93.1)
Monthly household income ($), mean (SD)§	3,190 (1442)
Other prenatal exposures, no. (%)	
Alcohol, exposure in early pregnancy only‖	345 (41.7)
Alcohol, low continuous exposure during pregnancy‖	18 (2.2)
Alcohol, moderate or high continuous exposure during pregnancy‖	40 (4.8)
Mother smoked during pregnancy¶	103 (12.6)

*Birth order for children based on children still living at the time of the birth of the child enrolled in the study.
†Race reported by the family based on American Indian definition.
‡Mother's health from medical record.
§Household income was not reported for 16 participants.
‖Data on mother's alcohol consumption during pregnancy data were not available for 4 participants. Categories assigned as described previously.[25]
¶Data on mother's smoking during pregnancy were not available for 12 participants. Categories assigned as described previously.[25]

12 months, including EIW, were based on the International Study of Asthma and Allergy in Childhood (ISAAC) standardized questionnaire.[24] A child was considered to have EIW if his or her parents answered yes to the question, "In the past 12 months, has the child's chest sounded wheezy during or after exercise?" Parents were also queried at to whether their child had been diagnosed with asthma by a medical professional. A child was considered to have current physician-diagnosed asthma if the parent answered yes to both of the questions, "Has a doctor or other health care provider ever diagnosed the child with asthma?" and "Does the child still have asthma?"

Statistical analysis

RRs with 95% CIs were calculated by using binomial regressions in generalized estimating equations. Models included the following *a priori*–determined potential confounders and important covariates: neonatal wheeze, cough and fever, age, gestational age at birth, premature birth, season of birth, maternal asthma, race, neonatal tobacco smoke exposure, and birth order. We conducted analyses stratified by sex, and effect modification was tested by using a multiplicative interaction term. Analyses were conducted using SPSS, version 28 (IBM, Armonk, NY), and visualized in R, version 4.2.1.

RESULTS

Participants and descriptive data

The demographics of study participants and health outcomes (N = 831) are described in Table I.[25] For the most part, the children included in the analyses did not differ in demographics from those who were recruited for the PASS/ECHO study but not included in the analyses because of missing data (n = 1724). Exceptions were that the children who were included were *less likely* to be firstborn, have mothers who were older, and have mothers who smoked during pregnancy and *more likely* to report being of the White race and having mothers who graduated from high school (see Table E1 in the Online Repository at www.jaci-global.org). In addition, the children included were less likely to have neonatal runny nose or cold symptoms.

Neonatal rhinorrhea and wheeze were common at age 1 month (Table II). Neonatal rhinorrhea was equally common among females and males, but cough at the neonatal assessment was more common among females. Wheeze at age 4 to 11 years was more common among males. Participants with versus without neonatal rhinorrhea were more likely to have older siblings and less likely to be in the group of children whose mothers consumed alcohol early in pregnancy, although there was not an overall difference in those exposed to any versus no alcohol during pregnancy. Children with and without rhinitis did not differ in gestational age at birth, maternal age, race, maternal asthma, maternal depression, or sociodemographic variables (see Table E2 in the Online Repository at www.jaci-global.org).

Neonatal rhinorrhea and EIW and other asthma outcomes at age 4 to 11 years

In bivariable analyses, children with versus without neonatal rhinorrhea were more likely to have EIW at age 4 to 11 years

TABLE II. Health outcomes of study participants at school age (N = 831)

Health outcome	Females (n = 422)	Males (n = 409)
At birth, no. (%)		
Premature birth	43 (10.2)	30 (7.3)
At age 1 mo (in past 2 wk), no. (%)		
Runny nose or cold	77 (18.2)	64 (15.6)
Wheeze	68 (16.1)	68 (16.6)
Cough	**61 (14.5)**	32 (7.8)
Fever	30 (7.1)	34 (8.3)
At age 4-11 y (in past year), no. (%)		
EIW	17 (4.0)	25 (6.1)
Wheeze	24 (5.7)	**46 (11.2)**
Nighttime cough without cold	54 (12.8)	69 (16.9)
Runny nose without cold (rhinitis)*	83 (19.7)	87 (21.3)
Current physician diagnosed asthma	21 (5.0)	28 (6.8)
Emergency department visit for asthma	4 (0.9)	11 (2.7)
Ever hospitalized for asthma†	8 (1.9)	13 (3.2)

P value is significant (<.01) (set in boldface).
*There were 2 children (1 male and 1 female) with missing data on rhinitis at age 4 to 11 years.
†For children aged 4 to 11 years, a parent answered whether the child had ever been hospitalized for asthma.

TABLE III. RR for EIW and physician diagnosis of asthma with infant rhinorrhea controlling for $RMSSD_{QS:AS}$ (mediation analysis)

Condition	Infant rhinorrhea adjusted for covariates*	Infant rhinorrhea adjusted for covariates and $RMSSD_{QS:AS}$†	Mediation
EIW			
All children (n = 231)	7.91 (95% CI = 1.85-33.9)‡	5.99 (95% CI = 1.24-28.8)§	24%
Females only (n = 119)	32.3 (95% CI = 2.62-398)‡	16.0 (95% CI = 1.26-204)§	50%
Physician-diagnosed asthma			
All children (n = 231)	7.54 (95% CI = 1.50-37.8)§	5.79 (95% CI = 1.06-31.7)§	23%
Females only (n = 119)	23.6 (95% CI = 2.09, 266)§	8.77 (95% CI = 0.64-121)§	63%

*RR for EIW or physician-diagnosed asthma with neonatal rhinorrhea adjusted for neonatal cough, wheeze and fever, sex, maternal asthma, gestational age at birth, preterm birth, season of birth, age of HRV and asthma outcome assessment, AI/AN race, exposure to ETS in infancy, and birth order.
†Model includes the same variables as in the column to the left and also $RMSSD_{QS:AS}$.
‡$P < .01$.
§$P < 05$.

(Fig 2, *A*). They were also more likely to have other asthma symptoms. Children with neonatal wheeze were more likely to have EIW and other asthma outcomes later in childhood (Fig 2, *B*). In a model adjusting for neonatal wheeze, cough and fever, age at asthma outcome assessment, gestational age at birth, premature birth, season of birth, maternal asthma, American Indian/Alaska Native race, neonatal environmental tobacco smoke exposure, and birth order, neonatal rhinorrhea predicted EIW at age 4 to 11 years (RR = 2.22 [95% CI = 1.04-4.73]; $P = .040$). In stratified analyses, the association was observed among female children (RR = 3.38 [95% CI = 1.23-9.29]; $P = .018$) but not among male children (RR = 1.39 [95% CI = 0.39-4.91]; $P = .61$) ($P_{interaction} = .12$). Overall, the risk factor pattern for EIW appeared to differ between sexes (Fig 2, *C*). For example, being third or later in birth order was only (inversely) associated with EIW among the males ($P_{interaction} = .003$).

Neonatal $RMSSD_{QS:AS}$, neonatal rhinorrhea, and EIW at age 4 to 11 years

HF-HRV data in AS and in QS were available for 231 of the 831 children with complete neonatal and childhood health data. The demographic characteristics of these 231 children did not differ from those of the children who did not have HF-HRV data in AS and in QS, except that children with versus without these data were less likely to have low alcohol exposure early in pregnancy and rhinitis symptoms at age 4 to 11 years (see Table E3 in the Online Repository at www.jaci-global.org). Although there was no differences between these 2 groups in either the prevalence of neonatal rhinorrhea or EIW at age 4 to 11 years, the associations between neonatal rhinorrhea and EIW were observed among the children with both AS and QS RMSSD data (RR = 7.40 [95% CI = 1.76-31.0]; $P = .006$) and not among those without these data (RR = 1.33 [95% CI = 0.50-3.43]; $P = .57$) ($P_{interaction} = .095$). In contrast, neonatal wheeze predicted EIW among those without AS and QS data (RR = 3.25 [95% CI = 1.52-6.91]; $P = .002$) but not among those with such data (RR = 1.18 [95% CI = 0.20-7.03]; $P = .85$) ($P_{interaction} = .21$). Models are visualized in Fig E1 (in the Online Repository at www.jaci-global.org).

The median ratio $RMSSD_{QS:AS}$ was 1.00 [IQR = 0.85-1.22]. $RMSSD_{QS:AS}$ did not differ by child's sex, birth order, or race; maternal asthma or depression; sociodemographics; or prenatal exposures to alcohol or smoke (see Table E4 in the Online Repository at www.jaci-global.org). In bivariate analyses, higher $RMSSD_{QS:AS}$ values were associated with increased risk of EIW and physician-diagnosed asthma at age 4 to 11 years (Fig 3). In multivariable analyses with adjustment for neonatal cough, wheeze and fever, sex, maternal asthma, gestational age at birth, premature birth, season of birth age of HRV and asthma

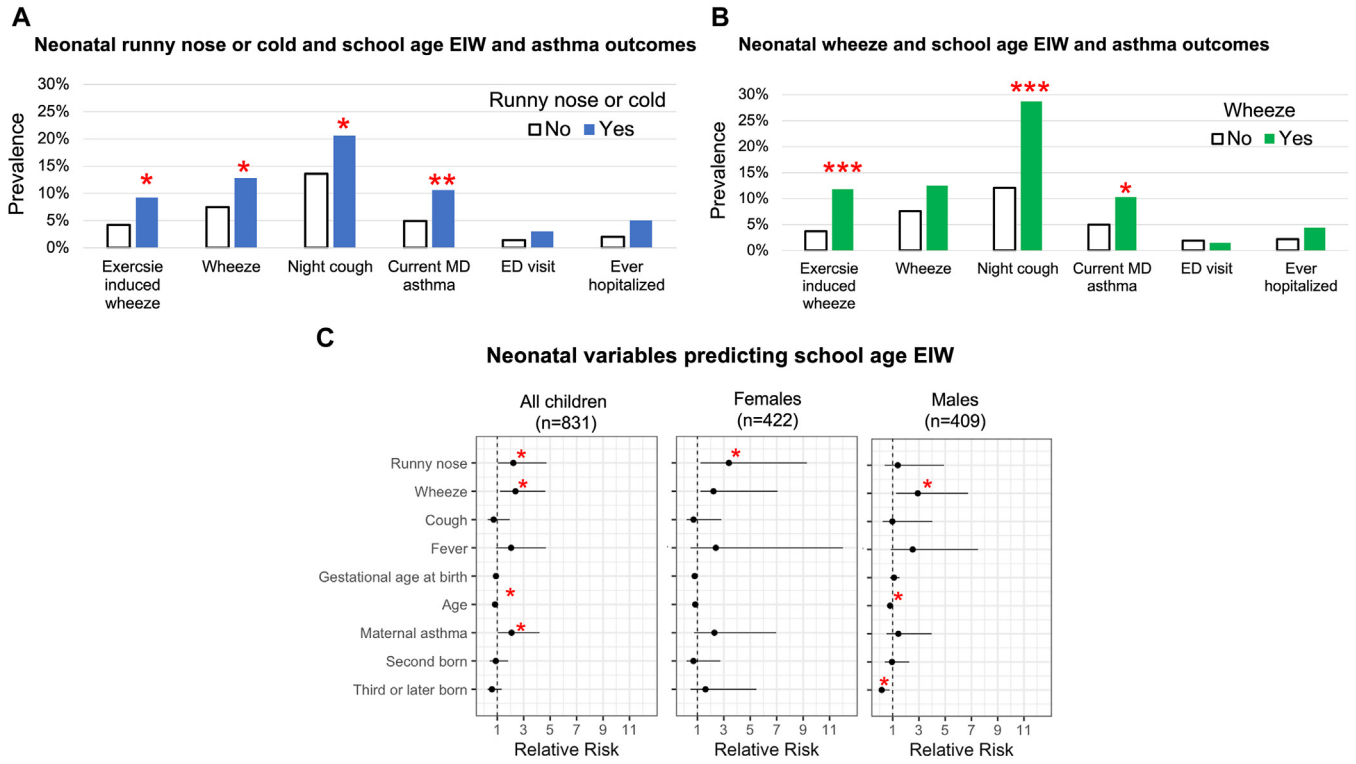

FIG 2. EIW and other asthma outcomes at age 4 to 11 years (N = 831 subjects) with neonatal rhinorrhea or cold (**A**), neonatal wheeze (**B**), and neonatal variables predicting EIW and other asthma outcomes at age 4 to 11 years (**C**) in a multivariable model controlling for wheeze and other symptoms at age 1 month and other variables depicted, along with season, premature birth, and race. **P* < .05; ***P* < .01; ****P* < .001. *ED,* Emergency department; *MD,* physician.

outcome assessment, American Indian/Alaska Native race, environmental tobacco smoke exposure in infancy, and birth order, an increase in $RMSSD_{QS:AS}$ IQR predicted both EIW (RR = 2.36 [95% CI = 1.34-4.15]; *P* = .003) and physician-diagnosed asthma (RR = 1.89 [95% CI = 1.10-3.25]; *P* = .020). These associations were of even greater magnitude among the female children alone (in the case of EIW, RR = 4.54 [95% CI = 1.09-19.0]; *P* = .038, and in the case of physician diagnosis of asthma, RR = 6.19 [95% CI = 1.15-33.4]; *P* = .034]) (visualized in Fig E2 in the Online Repository at www.jaci-global.org). The multivariable models failed to converge among the males, among whom there were only 3 and 2 children with EIW and physician-diagnosed asthma, respectively.

In multivariable models, an IQR increase in $RMSSD_{QS:AS}$ was not statistically significantly associated with neonatal rhinorrhea (prevalence ratio [PR] = 1.16 [95% CI = 0.84-1.62]; *P* = .37); however, in analyses stratified by sex, the association was statistically significant among the females (PR = 1.68 [95% CI = 1.06-2.68]; *P* = .029), but not among the males (PR = 0.75 [95% CI = 0.34-1.46]; *P* = .39). In mediation analyses, inclusion of $RMSSD_{QS:AS}$ in models as a potential mediator diminished the magnitude of the effect estimate for neonatal rhinorrhea predicting EIW and physician-diagnosed asthma (Table III).

The combination of infant rhinorrhea and $RMSSD_{QS:AS}$ in identifying future EIW and physician-diagnosed asthma was tested in females. Among females with neonatal rhinorrhea, the areas under the receiver operating characteristic curves for $RMSSD_{QS:AS}$ identifying EIW and physician-diagnosed asthma were high in magnitude and statistically significant (Fig 4). Similarly, the females with both infant rhinorrhea and $RMSSD_{QS:AS}$ in the highest tertile were more likely to have EIW and physician-diagnosed asthma (Fig 4).

DISCUSSION

We observed that neonatal rhinorrhea predicted EIW and current physician diagnosis of asthma at school age. These associations were observed even after adjusting for potential indicators of current infection (neonatal wheeze, cough, and fever), suggesting a noninfectious mechanism. Among a subset of children for whom we had HRV measured in both QS and AS, $RMSSD_{QS:AS}$, used as an indicator of PNS activity, was higher among females with neonatal rhinorrhea and predicted EIW and physician diagnosis of asthma in later childhood. When included as a potential mediator in statistical models, $RMSSD_{QS:AS}$ led to a decrease in the magnitude of the associations between neonatal rhinorrhea and EIW, suggesting involvement of the PNS in the mechanism connecting infant rhinorrhea to airway hyperreactivity later in childhood. In addition, the female children with both higher $RMSSD_{QS:AS}$ and rhinorrhea at age 1 month were at higher risk of developing EIW and having a physician diagnosis of asthma 4 to 11 years later.

These findings in the PASS/ECHO cohort further support our previous findings linking rhinorrhea symptoms in infancy to symptoms of airway hyperreactivity in later childhood and provide support of an underlying PNS mechanism connecting

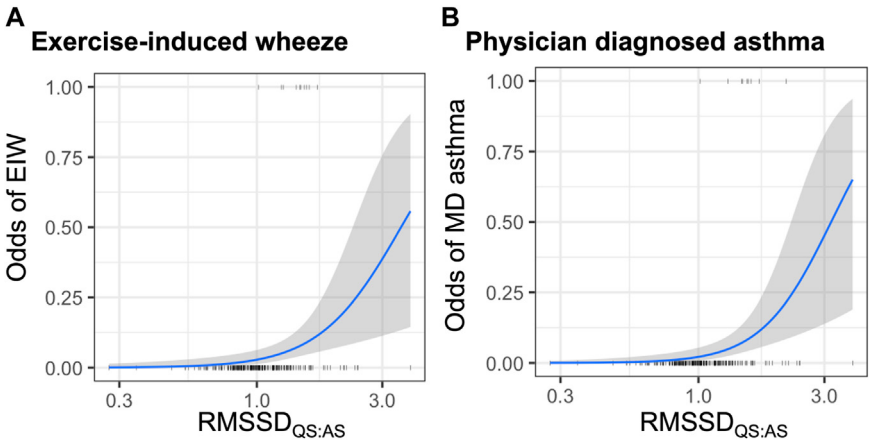

FIG 3. Association between $RMSSD_{QS:AS}$ in infancy and EIW (**A**) and physician (MD)-diagnosed asthma (**B**) at age 4 to 11 years (n = 231).

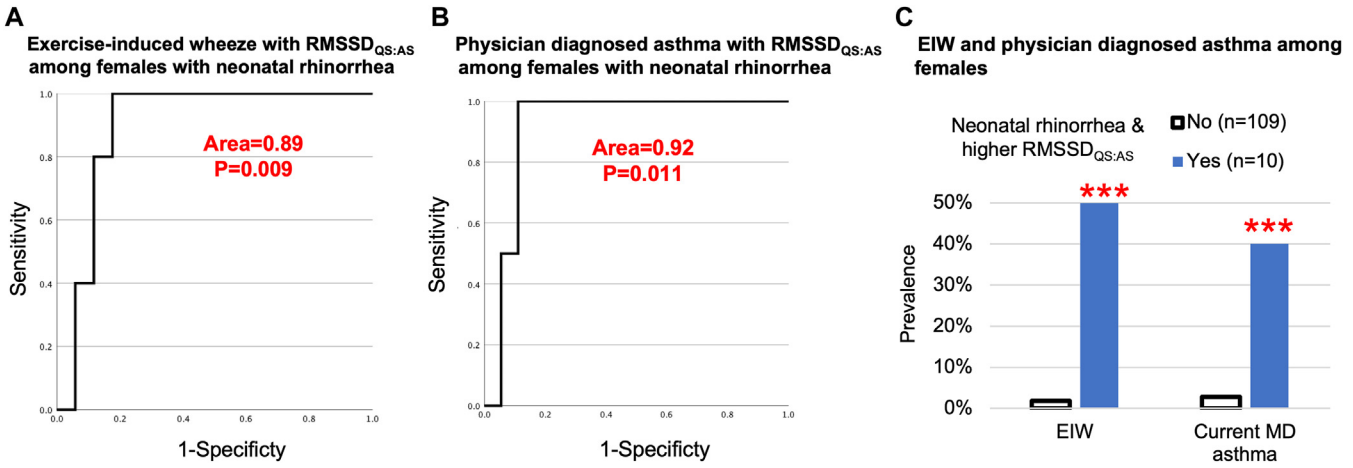

FIG 4. Receiver operating characteristic curves for $RMSSD_{QS:AS}$ identifying EIW (**A**) and physician (MD)-diagnosed asthma (**B**) among females with neonatal rhinorrhea. **C**, Prevalence of EIW and MD-diagnosed asthma at age 4 to 11 years among females with neonatal rhinorrhea and $RMSSD_{QS:AS}$ in the highest tertile. ***$P < .001$

them. Furthermore, the findings among this cohort of predominantly White and American Indian/Alaska Native children corroborate previous findings observed among a cohort of Black and Latinx children in NYC,[12] thus increasing the generalizability of the findings. The findings also are in keeping with the findings of several other relatively small studies of older children that have shown cross-sectional associations with increased HRV among children who have asthma or are at risk of having asthma as compared with controls.[26,27] In addition, there have been cross-sectional studies in adults showing positive correlations between HRV and bronchial hyperreactivity.[28,29] Importantly, our findings link infant measures of increased PNS activity to subsequent development of EIW, suggesting that PNS dysregulation linked to asthma can begin early in life and could be used to identify infants for primary prevention interventions.

An important feature of our findings is that the subset of 231 children for whom we had HRV data collected in both QS and AS appeared to be more susceptible to childhood EIW with neonatal rhinorrhea than children with data regarding only 1 sleep stage recorded. Our study was not originally designed to collect HRV in both sleep stages for all children; therefore, the subset for whom we had data collected in both stages was a convenience sample. The demographics among the 2 groups were similar, and why some children demonstrated sleep in both stages whereas some only demonstrated a single sleep stage is unclear. The sleep stage that was most frequently missing was QS. Sleep architecture of the newborn is specific, with AS often occurring at sleep onset. It is conceivable that a developmental factor could prevent or slow some children from switching effectively from AS to QS and that the developmental factor is also associated with decreased susceptibility to EIW development via PNS dysregulation. It will be important to evaluate this with future studies collecting data in both sleep stages for all children and evaluating the time to transition from AS to QS. Fortunately, with automated breathing rate variability methods for determining sleep stage, this could be done relatively easily in real-time to ensure capture of both sleep stages or the data collected overnight with a wearable monitor.[20]

As in our previous findings, the associations were observed among female children but not among male children. Although the underlying biologic reasons are mostly not understood, there

are known sex differences in asthma.[30] Although childhood asthma is predominant in males, the incidence of asthma among females rises significantly starting at puberty, and at middle age, asthma becomes more common among females than males. Some of the hypothesized reasons behind the male predominance of asthma in childhood include (1) a higher prevalence of atopy in males; (2) dysanapsis, which is a reduced relative airway size compared to lung volume in male children versus in female children; and (3) differences in reported symptoms between female and male children (a higher number of reports of wheeze in males).[31] In our study, the prevalence of a current diagnosis of asthma was higher among males; however, the association between dysregulation of the ANS and EIW is predominant among females, possibly supporting a nonatopic mechanism driving sex differences.

With further validation, these findings could have important public health and clinical utility. Relatively easy early-life screening tools for children at risk of developing EIW could be implemented, as could monitoring of these children for the development of asthma. Identification of an asthma phenotype with a nonallergic etiology could also have a significant impact on therapeutic management. Although the use of anticholinergic treatment in asthma management is currently limited, it could be redefined in patients with demonstrated heightened parasympathetic activity.[32] For example, a recent trial of ipratropium bromide in young children showed success in reducing recurrent wheeze.[33]

We recognize limitations to our study. First, the sample for $RMSSD_{QS:AS}$ analysis was relatively small, and the reduction in sample size from the larger cohort appeared to not be at random. This nonrandomness should be investigated in future studies, as it may provide even further insight into the role of ANS development in the link between neonatal PNS signaling and future airway hyperreactivity. Another limitation was the use of HRV data from both newborns and 1-month-olds, as maturation of the ANS at that age is rapid. Models were adjusted for the time point at which the data were collected. We also acknowledge that the use of an automated respiration variability method to classify sleep states could have resulted in a minor portion of the epochs being misclassified; however, the methods utilized and reported in this article and by others have demonstrated good (~80%) concordance between sleep states classified using these automated methods and polysomnographic and behavioral state coding.[20,34] An additional limitation is that EIW was assessed by questionnaire report from the parent. A small cross-sectional study in adults found higher HRV among subjects who had airway hyperreactivity after a methacholine test but there are no data in children.[35] Objectively measuring exercise-induced bronchospasm will be an important next step to test for associations with neonatal PNS dysregulation. We also acknowledge that we did not measure PNS activity directly in subjects' lungs in this study and that our supposition is based on HF-HRV, which is an indirect assessment of PNS signaling.

Conclusions

Collectively, these findings provide substantial additional support connecting elevated PNS activity in infancy to infant rhinorrhea and airway hyperreactivity at school age, and they suggest that a combination of infant HRV and rhinorrhea symptoms could be useful tools to predict future exercise-induced asthma development in females. By establishing this novel paradigm whereby altered ANS in infancy leads to exercise-induced asthma morbidity at school age, we expect to eventually be able to identify children early in life for interventions to prevent future asthma-related morbidity and improve therapeutic management.

DISCLOSURE STATEMENT

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Key messages

- **There is increasing evidence linking infant rhinorrhea to a risk of developing school-age EIW via a PNS pathway.**
- **In a prospective study, neonatal rhinorrhea predicted EIW at ages 4 to 11 years, specifically among females. The ratio of PNS related HRV measured in QS to AS in infancy acted as a mediator of this association among females.**
- **These findings support a connection between infant dysregulation of the PNS and the development of EIW and other asthma morbidity among females, which could aid in the development of future interventions.**

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