Lung sound analysis for predicting recurrent wheezing in preschool children

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Background: In young healthy children, assessing airflow limitation may be difficult because of narrowing of the airways, which is a pathology of asthma, and responsiveness to bronchodilators.

Objective: We investigated whether lung sound analysis could predict the development of recurrent wheezing (RW), which is one of the signs of asthma.

Methods: In healthy children aged 3 to 24 months, we recorded and analyzed lung sounds before and after inhalation of bronchodilators and conducted a questionnaire survey. The children were followed up and assessed for the development of RW at age 3 years.

Results: Of the 62 patients analyzed, 19 (30.6%) developed RW. The parameters ratio of power and frequency at 50% of the highest frequency of the dB power spectrum (RPF_{50}) and ratio of power and frequency at 75% of the highest frequency of the dB power spectrum (RPF_{75}), calculated by lung sound analysis, were lower in the RW group, with odds ratios of 0.77 (95% CI = 0.61-0.98) and 0.81 (95% CI = 0.66-0.99), respectively. The rate of change of lung sound analysis parameters after bronchodilator inhalation did not differ among the participants as a group; however, in the subgroup of children with a history of atopic dermatitis, the fourth area under the curve (B_4) divided by the total area under the curve of 100 Hz to the highest frequency of the dB power spectrum (A_T) and difference between the values of the ratio of power and frequency at 50% of the highest frequency of the dB power spectrum (ΔRPF_{50}) were elevated in the RW group ($P = .015$ and $P = .041$, respectively). In the subgroup of children with total a IgE level greater than 20 kUA/L, the sensitivities and specificities for predicting the development of RW were 85.7% (95% CI = 48.7-99.3) and 68.8% (95% CI = 44.4-85.8), respectively, when the cutoff value of ΔRPF_{50} was set at 10.5%.

Conclusion: The method of lung sound analysis allows noninvasive assessment of the airway, including airway hypersensitivity, in young children and may predict the risk of development of RW. (J Allergy Clin Immunol Global 2024;3:100199.)

Key words: *Asthma, airway hypersensitivity, infant, lung sound analysis, risk factor*

Asthma is characterized by chronic inflammation of the airways.[1] Patients with asthma have increased airway hypersensitivity due to chronic airway inflammation and develop symptoms such as wheezing, coughing, and shortness of breath.[2] Assessment of airway hypersensitivity is an important indicator of asthma. Airway hypersensitivity is assessed by evaluating the response to bronchoconstrictors or bronchodilators.[1] However, respiratory function tests such as spirometry may be difficult to perform routinely in the 0- to 2-year-old age group.[3,4] Therefore, the diagnosis of asthma in infancy is based on an episode of wheezing and confirmation of reversible variable airway obstruction that can be confirmed by diagnostic treatment tests with inhaled bronchodilators or corticosteroids.[4]

Wheezing is an acoustic onomatopoeic or musical sound produced by the vibration of the bronchial walls; it occurs when the respiratory effort required to maximize airflow through the airways is exceeded.[5] Wheezing is a common clinical finding in early childhood,[6] and the mixture of phenotypes in this age group makes the diagnosis of asthma in younger children difficult.[7] To diagnose asthma, it is necessary to develop an objective indicator that can be used in young children.[8]

We previously established a method for assessing airway hypersensitivity using the lung sound analysis method and its usefulness in children.[9-11] Appropriate assessment of airway hypersensitivity, which is one of the major signs of asthma, is useful for evaluating patients who are at a high risk of developing asthma in the future and should be treated. However, whether airway hypersensitivity assessed by using lung sounds can predict the subsequent development of asthma is unclear.

Therefore, this study aimed to assess airway hypersensitivity in healthy infants by using lung sound analysis and create a cutoff for predicting recurrent wheezing (RW) by age 3 years.

METHODS

Study participants

This was a prospective, cross-sectional, multicenter study of a cohort of healthy children. Healthy children aged 3 to 24 months who received medical checkups at the National Hospital Organization Yokohama Medical Center, Tokai University Hospital, or Dokkyo Medical University Hospital from January 1, 2012, to

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Received for publication February 11, 2023; revised September 22, 2023; accepted for publication September 26, 2023.

Available online December 7, 2023.

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2772-8293

https://doi.org/10.1016/j.jacig.2023.100199

Abbreviations used

A_3: Third area under the curve
ATS-DLD: American Thoracic Society Division of Lung Disease
A_T: Total area under the curve of 100 Hz to the highest frequency of the dB power spectrum
AUC: Area under the curve
B_4: Fourth area under the curve
ΔRPF_{50}: Difference between the values of the ratio of power and frequency at 50% of the highest frequency of the dB power spectrum
ΔRPF_{75}: Difference between the values of the ratio of power and frequency at 75% of the highest frequency of the dB power spectrum
ROC: Receiver operating characteristic
RPF_{50}: Ratio of power and frequency at 50% of the highest frequency of the dB power spectrum
RPF_{75}: Ratio of power and frequency at 75% of the highest frequency of the dB power spectrum
RW: Recurrent wheezing
Slope: Roll-off from 600 to 1200 Hz

March 31, 2016, and whose parents agreed to participate were included in the study. The exclusion criteria were being born before 37 weeks and/or weighing less than 2500 g, having a congenital disease, and undergoing treatment for a chronic respiratory disease.

Study protocol

First interview. First, a medical interview was conducted, and auscultation by a pediatric allergist confirmed the absence of abnormal sounds such as rales or wheezing and that blood oxygen saturation was normal. Respiratory sounds were recorded during resting breathing. Next, the infants were made to inhale bronchodilators. The bronchodilator used was procaterol, a short-acting β_2-stimulant, at the dose indicated in the Japanese guidelines; it was inhaled using a nebulizer. Fifteen minutes after inhalation, respiratory sounds were recorded again during resting breathing. Blood tests were then performed on the children. Additionally, parents were asked to fill out a questionnaire based on the American Thoracic Society Division of Lung Disease (ATS-DLD) questionnaire[12]; and in cases of unclear answers, the doctor conducted additional surveys.

Second interview. When the child reached 3 years of age, an ATS-DLD–based questionnaire was mailed to the parents for them to complete. In cases of unclear answers, the doctor confirmed the answers by telephone interview.

Questionnaire

We used our original questionnaire, which was translated from the ATS-DLD into Japanese (see Table E1 in the Online Repository at www.jaci-global.org); the questionnaire examined the presence or absence of current respiratory infections, history of wheezing (which is recognized as a risk factor for childhood asthma), respiratory infection–related factors, and atopy-related factors. We defined the presence of passive smoking as the presence of a smoker in a family living together. Pet keeping was defined as keeping a cat, dog, or other hairy animal indoors, and a positive family history of allergy was defined as a history of allergic disease in a second-degree family member.

Definition of RW

To determine RW, we asked the question, "How many times has your child had wheezing in the chest?" Repetitive wheezing was defined as the presence of 3 or more episodes of wheezing.

Calculation method for lung sound parameters

All participants underwent collection of lung sounds as previously described.[10,13] Lung sounds were recorded for at least 10 breaths by using a handheld microphone in a quiet booth. The microphone was placed on the upper right anterior chest at the second intercostal space along the midclavicular line. The sound of the inspiration phase was analyzed by using an LSA-2008 sound spectrometer (Kenz Medico Co, Saitama, Japan).

The sound-amplifying unit was effective for analyzing sounds in the range from 100 to 2,500 Hz. The recorded sounds were analyzed by using fast Fourier transformation. The sampling frequency was 10,240 Hz, and the spectra were obtained by using a Hanning window. The sounds were displayed as a spectrograph. The dBm values were plotted on the y-axis, and the Hz values were plotted on the x-axis.

To evaluate the dBm-based spectrum images, we decided to set the zero point of the Y-axis (in dBm) based on the background noise power in each patient. In most cases, the value found was approximately –90 dBm. In this article, the zero level (0 dB of the lung sound spectrum) was visually corrected based on the lung sound spectra in each sample before the zero point (the frequency at 0 dB) was decided (see Fig E1, *A* and *B* in the Online Repository at www.jaci-global.org).[14]

The zero and zero points were used to calculate the area under the curve (AUC) In the sound spectrum. The roll-off from 600 to 1200 Hz (henceforth referred to as slope) indicates the roll-off of the middle spectrum curve (–dB/octave).[15,16] Total area under the curve of 100 Hz to the highest frequency of the dB power spectrum (A_T), third area under the curve (A_3), and fourth area under the curve (B_4), were conventionally calculated according to the dB and Hz (1 arbitrary unit [dB • Hz] on a spectrum image). The spectrum curve indices (A_3/A_T, B_4/A_T, ratio of power and frequency at 75% of the highest frequency of the dB power spectrum [RPF_{75}], and ratio of power and frequency at 50% of the highest frequency of the dB power spectrum [RPF_{50}]) were also calculated (see Fig E2, *A-C* in the Online Repository at www.jaci-global.org). A 5-point moving average was used as a smoothing technique to determine the suitable dB value for identifying checkpoints in the slope of each sound spectrum.

In this study, 3 lung sound samples from at least 10 samples were obtained. In each institute, 2 or more physicians who were licensed pediatricians discussed the selection of sound samples without noise and with the same sound spectrum size for each individual. After the zero point had been chosen, personal lung sounds were automatically calculated using an in-house calculation software program.[10,13] The median value from the 3 tidal breath samples was determined as the final result for each patient.

The parameter calculated from breath sounds before inhalation of bronchodilators was defined as the prevalue, and the parameter calculated from the breath sounds after inhalation of bronchodilators was defined as the postvalue. For each parameter, the

difference between the prevalue and postvalue divided by the prevalue was used as the change rate, and Δ was written in front of the parameters.

IgE antibody levels

Nonspecific IgE antibodies and allergen-specific IgE antibody titers against egg white and house dust mites were measured by using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). Specific IgE antibody levels of 0.35 kUA/L or more were considered positive. For total IgE levels, data from healthy Japanese infants were used,[17] with levels of 20 kUA/L for children younger than 1 year and 30 kUA/L or higher for children aged 1 to 3 years considered positive.

End points

The primary end point was onset of RW at age 3 years. The subanalysis was stratified according to the atopic factors.

Statistical analyses

Categoric data are presented as numeric values and percentages. Continuous data are reported as medians and interquartile ranges. The backgrounds of the participants were compared between the no-RW and RW groups. Categoric data were compared using the Fisher exact test, and continuous variables were compared using the Wilcoxon rank sum test. Factors for RW before age 3 years were analyzed using logistic regression models with the forced entry method. The receiver operating characteristic (ROC) curve is a plot of sensitivity as a function of 1-specificity for all possible cut points of the RW up to age 3 years. The Youden index, which is defined as the maximum vertical distance between the ROC curve and the diagonal or chance line, was calculated as the sum of sensitivity plus specificity. All statistical analyses were performed using SPSS, version 27 (IBM Japan, Tokyo, Japan). Statistical significance was set at P less than .05.

Ethics statement

The study protocol was approved by the ethical review committees of Tokai University Hospital (approval no. 11R-158 [approval date December 21, 2011], approval no. 14R-133 [approval date December 15, 2015], and approval no. 17R-161 [approval date October 10, 2017]). Written informed consent was obtained from the parents of each child.

RESULTS

We recruited 79 healthy infants and excluded those with RW or physician-diagnosed asthma at the time of the first visit (n = 6). Following application of the exclusion criteria, 73 participants were enrolled after informed parental consent had been obtained. We followed 62 children until age 3 years, and those children were included in the analysis (Fig 1).

Characteristics

Of the 62 participants, 27 (44%) were male; the mean age at the first visit was 7 months (interquartile range = 7.0, 9.0) (Table I). In all, 19 children (30.6%) developed RW at age 3 years (Table II).

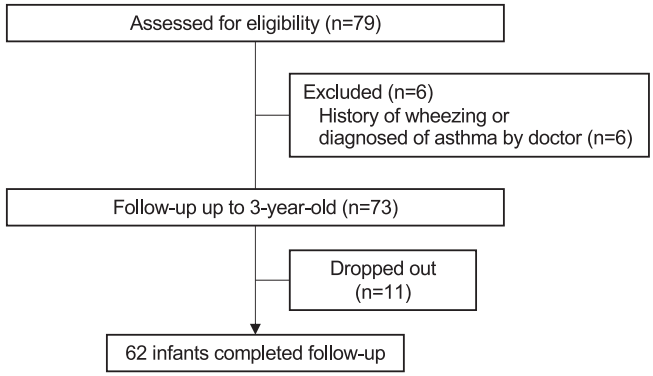

FIG 1. Flowchart of participant selection.

No differences in age, sex, or weight at the time of inclusion were observed between the RW group and the no-RW group, although height was lower in the RW group, with an odds ratio of 0.88 (95% = 0.79-0.99).Other risk factors for childhood asthma —exposure to passive smoking, history of pet ownership, and family history of allergies–did not differ significantly between the 2 groups. With regard to hematologic data, no difference in nonspecific IgE levels or mite-specific IgE antibody positivity was observed between the RW and no-RW groups. However, the number of patients with positive egg white–specific IgE antibody levels was higher in the RW group, with an odds ratio of 1.70 (95% CI = 1.07-2.70).

Lung sound analysis parameters

Primary end point. No difference in A_3/A_T and B_4/A_T values was observed between the RW group and the no-RW group; however, the RPF_{50} and RPF_{75} values were lower in the RW group, with odds ratios of 0.77 (95% CI = 0.61-0.98) and 0.81 (95% CI = 0.66-0.99), respectively (Table III). After these parameters had been adjusted for age, sex, atopy, and family history of allergy, they were still lower in the RW group, with adjusted odds ratios of 0.72 (95% CI = 0.55-0.94) and 0.74 (95% CI = 0.57-0.96), respectively. No differences in $\Delta A_3/A_T$, $\Delta B_4/A_T$, ΔRPF_{50}, or difference between the values of the ratio of power and frequency at 75% of the highest frequency of the dB power spectrum (ΔRPF_{75}) were identified between the 2 groups (Fig 2).

The ROC curve analysis for predicting RW onset indicated a sensitivity of 68.4% (95% CI = 49.9-82.9), specificity of 72.1% (95% CI = 63.9-78.5), positive predictive value of 52.0% (95% CI = 38.0-63.0), negative predictive value of 83.8% (95% CI = 74.3-91.2), and accuracy of 71.0% (495% CI = 9.9-82.9), when an RPF_{50} value of 6.87 or RPF75 value of 7.25 was used as the cutoff (Fig 3).

Subanalysis. In the children with a history of atopic dermatitis at the time of inclusion (n = 12), the $\Delta B_4/A_T$ and ΔRPF_{50} values were higher in the RW group (n = 6) than in the no-RW group (P = .02 and P = .04, respectively). In the group with elevated total IgE and RW levels at the time of inclusion (n = 6), the ΔRPF_{50} values were higher than those of the other children (P = .02). The ROC curve analysis was performed to calculate the cutoff values of lung sound parameters that predict onset of RW with elevated IgE levels (Fig 4). The ROC curve analysis suggested that for children with elevated total IgE levels at inclusion (n = 23), the sensitivity was 85.7% (95% CI =

TABLE I. Participants' backgrounds

Characteristic	Overall
Infants, no. (%)	62
Age (mo), median (IQR)	7.0 (7.0, 9.0)
Male sex, no. (%)	27 (44)
Body weight (kg), median (IQR)	8.6 (7.7, 9.6)
Height (cm), median (IQR)	70.0 (67.1, 76.9)
Atopic dermatitis, no. (%)	12 (19.3)
Household smoke, no. (%)	13 (21.0)
History of RSV, no. (%)	2 (3.2)
Hospitalization for bronchitis or pneumonia, no. (%)	2 (3.2)
Family history of allergic disease, no. (%)	
Asthma	26 (41.9)
Atopic dermatitis	18 (29.0)
Allergic rhinitis	46 (74.2)
Pet keeping, no. (%)	
Dog	6 (9.7)
Cat	4 (6.5)
Laboratory test result	
Total IgE level (IU/mL), median (IQR)	13.2 (1.1, 30.7)
EW sIgE level > 0.35 U_A/mL, no. (%)	27 (43.5)
Der (Der p1) sIgE level > 0.35 U_A/mL, no. (%)	1 (1.6)

Der p 1, Dermatophagoides pteronyssinus peptidase 1; *EW*, egg white; *IQR*, interquartile range; *RSV*, respiratory syncytial virus; *sIgE*, specific IgE.

TABLE II. Differences in patient characteristics between no recurrent wheezers with no recurrence and wheezers with recurrence

	No recurrent wheezing	Recurrent wheezing	*P* value
Infants, no. (%)	43 (69.4)	19 (30.6)	
Age (mo), median (IQR)	7.0 (7.0, 9.0)	7.0 (7.0, 9.0)	.99*
Male sex, no. (%)	20 (46)	7 (41)	.34†
Body weight (kg), median (IQR)	8.9 (8.0, 10.0)	8.0 (7.7, 8.9)	.07*
Height (cm), median (IQR)	72.4 (67.6, 78.1)	68.0 (66.0, 72.0)	**.02***
Atopic dermatitis, no. (%)	6 (14.0)	6 (31.6)	.10†
Household smoke, no. (%)	8 (18.6)	5 (26.3)	.23†
History of RSV infection, no. (%)	2 (4.7)	0 (0)	.48†
Hospitalization for bronchitis or pneumonia, no. (%)	2 (4.7)	0 (0)	.48†
Family history of allergic disease, no. (%)			
Asthma	17 (39.5)	9 (47.4)	.75†
Atopic dermatitis	14 (32.6)	4 (21.1)	.28†
Allergic rhinitis	32 (74.4)	14 (73.7)	.63†
Pet keeping, no. (%)			
Dog	5 (10.9)	1 (4.5)	.39†
Cat	2 (4.3)	2 (9.1)	.44†
Laboratory test result			
Total IgE level (IU/mL), median (IQR)	15.0 (1.7, 27.1)	8.0 (0, 31.0)	.67*
EW sIgE level > 0.35 U_A/mL, no. (%)	15 (34.9)	12 (63.2)	**.02**†
Der (Der p 1) sIgE level > 0.35 U_A/mL, no. (%)	1 (2.3)	0 (0)	.69*

Boldface indicates statistical significance.
Der p 1, Dermatophagoides pteronyssinus peptidase 1; *EW*, egg white; *IQR*, interquartile range; *RSV*, respiratory syncytial virus; *sIgE*, specific IgE.
*Wilcoxon rank sum test.
†Fisher exact test.

48.7-99.3), the specificity was 68.8% (95% CI = 44.4-85.8), the positive predictive value was 54.5% (95% CI = 35.0-61.9), the negative the predictive value was 91.7% (95% CI = 73.7-98.4), and the accuracy was 73.9% (95% CI = 55.2-81.0) with a cutoff value of ΔRPF_{50} of 10.5% (Fig 5).

DISCUSSION

In assessing airway hypersensitivity in children with RW aged 3 years or less in a cohort of healthy infants associated with the inhalation of bronchodilators, changes in lung sound parameters were identified as a possible predictor of RW in some phenotypes.

The lung sound parameters that we used in this study, A_3/A_T and B_4/A_T, indicate the percentages of the total AUC of the lung sound spectrogram that are accounted for by the high-frequency region, respectively; RPF_{50} and RPF_{75} values indicate the slopes of the lung sound spectrogram in the high-frequency region, respectively.[13] In the children diagnosed with atopic asthma, bronchoconstriction induced by inhaled methacholine inhalation is observed as a decrease in A_3/A_T, B_4/A_T, RPF_{50}, and RPF_{75} values.[9,18] Moreover, inhalation of bronchodilators has been

TABLE III. Prevalues and postvalues and rate of change of each parameter of the lung sound analysis

Parametor of lung sound analysis	Overall (N = 62)					
	No-RW group (n = 43)	RW group (n = 19)	Crude OR (95% CI)	*P* value	Adjusted OR*† (95% CI)	*P* value
A_3/A_T (%), median (IQR)						
Prevalue	11.13 (9.60, 12.85)	11.60 (8.67, 13.40)	1.01 (0.83, 1.24)	.89	0.99 (0.79, 1.24)	.89
Postvalue	11.64 (9.23, 13.43)	13.99 (9.15, 15.65)	1.07 (0.91, 1.27)	.43	1.06 (0.89, 1.27)	.51
Rate of change ($\Delta A_3/A_x$)†	3.35 (-11.32, 23.65)	9.78 (-7.18, 26.59)	1.01 (0.99, 1.02)	.45	3.01 (0.53, 17.1)	.21
B_4/A_T (%), median (IQR)						
Prevalue	6.27 (5.36, 7.66)	6.88 (5.19, 7.71)	0.99 (0.72, 1.36)	.94	0.94 (0.66, 1.34)	.74
Postvalue	6.33 (5.03, 8.13)	7.50 (5.12, 9.46)	1.07 (0.86, 1.35)	.53	1.07 (0.85, 1.36)	.56
Rate of change ($\Delta B_4/A_T$)†	1.05 (-20.78, 36.84)	21.16 (-6.58, 35.84)	1.01 (0.99, 1.02)	.36	3.09 (0.69, 14.0)	.14
RPF_{50}						
Prevalue (dB/Hz), median (IQR)	8.22 (6.08, 10.20)	5.90 (4.91, 8.02)	0.77 (0.61, 0.98)	**.035**	0.72 (0.55, 0.94)	**.016**
Postvalue (dB/Hz), median (IQR)	8.03 (6.32, 10.50)	6.44 (5.18, 8.74)	0.87 (0.72, 1.05)	.15	0.81 (0.65, 1.02)	.07
Rate of change (ΔRPF_{50}) (%), median (IQR)†	-4.13 (-21.89, 23.34)	9.17 (-18.35, 36.39)	1.01 (0.99, 1.02)	.38	1.73 (0.55, 5.40)	.35
RPF_{75}						
Prevalue (dB/Hz), median (IQR)	8.30 (6.47, 9.74)	5.97 (4.81, 7.88)	0.81 (0.66, 1.00)	**.049**	0.74 (0.57, 0.96)	**.022**
Postvalue (dB/Hz), median (IQR)	8.35 (6.73, 11.00)	7.38 (5.50, 10.36)	0.93 (0.79, 1.09)	.36	0.88 (0.74, 1.06)	.17
Rate of change (ΔRPF_{75}) (%), median (IQR)†	-0.93 (-20.33, 45.48)	26.79 (-6.88, 47.78)	1.00(0.99, 1.01)	.53	1.41 (0.55, 3.57)	.48

IQR, Interquartile range; *OR*, odds ratio.
*Adjusted OR was adjusted for age, sex, body atopy, and family history of atopy.
†Change rates was calculated by the difference between the prevalue and the postvalue divided by the prevalue.

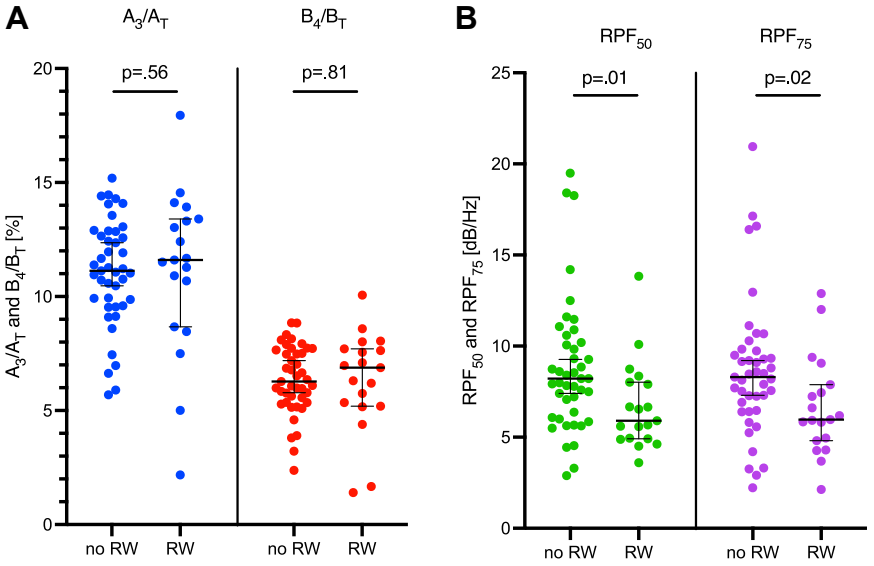

FIG 2. Participants' overall lung sound analysis parameters of A_3/A_T and B_4/A_T (**A**) and RPF_{50} and RPF_{75} (**B**). No differences in A_3/A_T and B_4/A_T were observed between the RW and no-RW groups, although the RPF_{50} and RPF_{75} values were lower in the RW group.

reported to restore these values to their original levels.[9] Hence, a decrease in these lung sound parameters indicates a decrease in airway diameter.

First, our data indicate no difference in A_3/A_T or B_4/A_T, whereas RPF_{50} and RPF_{75} were lower in children who had RW by age 3 than in those who did not have RW. This indicates that the AUC in the high-pitch range of the lung sound spectrum graph is similar, although the AUC of the spectrum graph in the high-pitch range decreased. This suggests that children with RW may have had airway narrowing before the onset of wheezing. Although this is an acoustic speculation (because it is difficult to measure the actual airway diameter), it may suggest that there is a population of healthy children. The narrowing of the airways is caused by environmental pollutants and sensitization to allergens, which ultimately leads to one of the phenotypes of asthma.[19] Therefore, children with airway narrowing in early childhood may have been more sensitive to RW later in life. Whether intervention is necessary for such children is a subject for future studies.

Second, our data suggest that changes in lung sound parameters after bronchodilator inhalation in healthy children are not involved in the subsequent development of RW. Thus, airway hypersensitivity is not universally present in all children who develop RW. However, when the study was limited to children who were diagnosed with AD at the time of inclusion, both $\Delta B_4/A_T$ and ΔRPF_{50} were elevated. The increase in these parameters

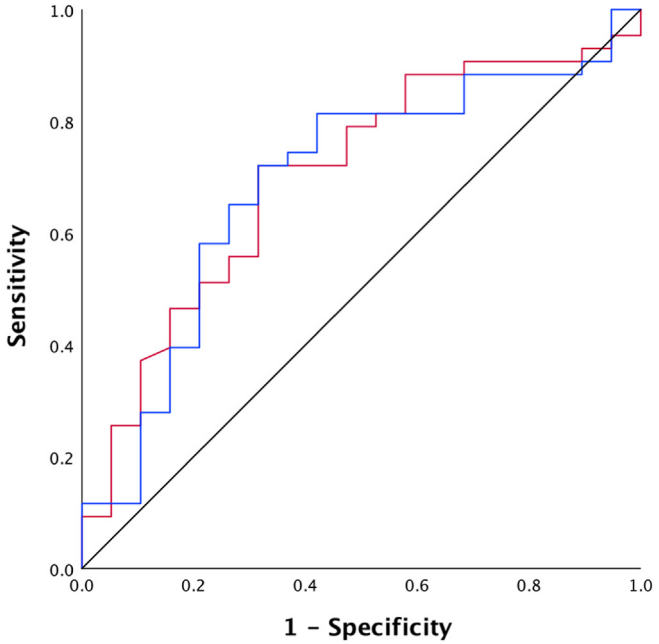

FIG 3. ROC curves for RPF_{50} (*red*) and RPF_{75} (*blue*) values for the whole population. The AUC values of RPF_{50} (*red*) and RPF_{75} (*blue*) were 0.70 (95% CI = 0.56-0.84) and 0.69 (95% CI = 0.55-0.84), respectively.

allergic diseases such as atopic dermatitis.[1] It is known that there are several populations with different wheezing phenotypes in young children, and not all children with RW develop asthma.[6,21] Our data suggest that children with airway hypersensitivity in a population with an atopic background may be at a higher risk of developing RW. However, the number of children with a history of atopic dermatitis in our cohort was small, and the odds ratios could not be calculated.

Furthermore, in investigating the establishment of a cutoff value combined with the objective parameters, predicting the onset of RW in children with high total IgE levels may be possible by calculating the rate of change in lung sound parameters before and after bronchodilator inhalation. The normal value of total IgE is known to vary depending on race and age,[22] and the normal value in Japanese children used in this study was lower than the value proposed internationally.[23] Although the total IgE level is only one of the factors in the development of asthma, our data suggest that children with a predisposition to atopy who exhibit elevated IgE levels may have acquired airway hyperresponsiveness from early childhood.

Importantly, our participants had no respiratory findings such as respiratory rales or pulse oximeter abnormalities at the time of lung sound recording. This was also true after inhalation of bronchodilators, indicating that the changes were slight and difficult to detect with the devices commonly used in the clinical

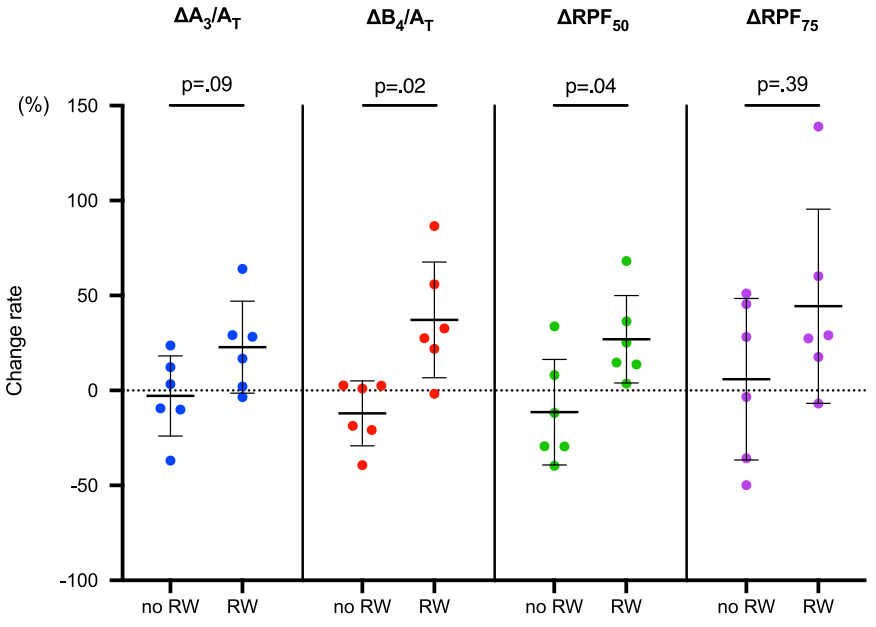

FIG 4. The rate of change of each lung sound parameter before and after bronchodilator inhalation; the $\Delta B_4/B_T$ and ΔRPF_{50} were higher in the RW group than in the no-RW group, with *P* values of .02 and .04, respectively.

suggests that bronchial narrowing improved in response to bronchodilators. Thus, children with a history of atopic dermatitis and subsequent RW may have airway hypersensitivity even before the onset of wheezing. Atopic dermatitis is associated with allergic diseases such as asthma and has been shown to be a "gateway" to allergic diseases.[20] It may be possible to screen children at a high risk of RW development by lung sound analysis if the target population is limited to children at high risk of development of setting. This means that our method of lung sound analysis has the potential to assess the airway objectively and noninvasively in a way that was not possible by existing examinations.

The limitations of this study are as follows. First, the number of study participants was small, making subanalysis difficult. The present results suggest that children with airway hyperresponsiveness during infancy may be a subset of children with RW. Therefore, it is necessary to conduct a larger cohort study. Second,

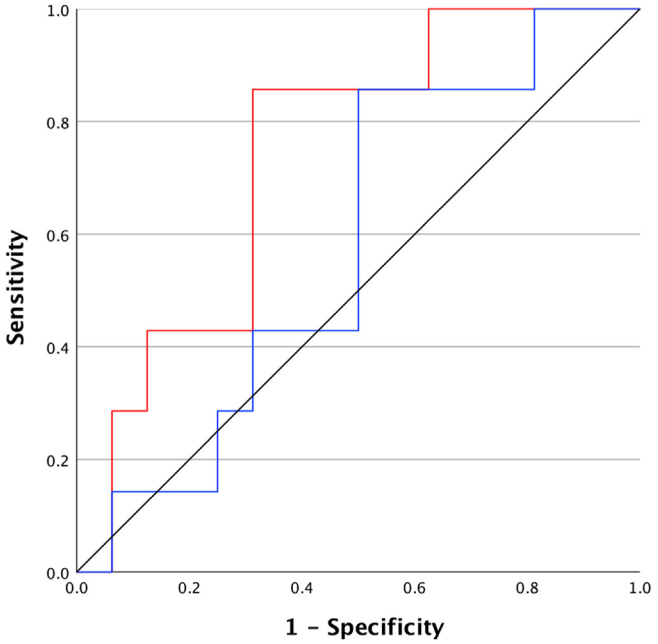

FIG 5. ROC curves for RPF_{50} (*red*) and RPF_{75} (*blue*) in the group with an elevated total IgE level. The AUC values of RPF_{50} (*red*) and RPF_{75} (*blue*) were 0.74 (95% CI = 0.53-0.95) and 0.58 (95% CI = 0.34-0.82), respectively.

this study was based on data regarding children no older than 3 years. At this age, it is difficult to assess respiratory function, and longer-term data need to be examined to track the development of asthma. Third, our end point was based on RW as reported by their parents. This is because the number of children diagnosed with asthma before age 3 years was small (n = 6), making statistical analysis difficult. When diagnosis of asthma by a physician was used as the dependent variable, no difference in the change in breath sounds caused by bronchodilators was noted between the RW and no-RW groups (data not shown). This may be attributed to the difficulty in diagnosing asthma in infancy and to the fact that pediatricians tend to hesitate to make a definite diagnosis of asthma in infancy. Data on underdiagnosis of pediatric asthma are limited,[24,25] especially in young children, making the issue difficult to verify. Throughout this study, we considered the fact that the generalizability and cost-effectiveness of this pulmonary sonar intervention as a surrogate for asthma prediction in young children are limited by the small size and single-center nature of the study, as well as by the ability of a single intervention to mimic the complex heterogenous presentation of pediatric asthma.

In conclusion, predicting the development of RW in some phenotypes, possibly in children with atopic background, may be difficult. In the future, our lung sound analysis technique, as one of the auscultatory findings, may lead to an accurate decision regarding early intervention in patients at a high risk of developing asthma.

DISCLOSURE STATEMENT

Supported by the Environmental Restoration and Conservation Agency of Japan in fiscal years 2009-2017 and the Dokkyo Medical University Young Investigator Award (grant number 2019-11 [to M.M.]).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Clinical implications: Lung sound analysis allowed noninvasive assessment of airflow limitation and response to bronchodilators. The calculated lung sound parameters could be used to predict the future onset of recurrent wheezing.

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