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Computerized respiratory sounds in paediatrics: A systematic review

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ABSTRACT

Background: Diagnosing and monitoring of children with respiratory disorders is often challenging. Respiratory sounds (RS) are simple, non-invasive and universally available measures that are directly related to movement of air, within the tracheobronchial tree. Thus, RS may be valuable indicators of respiratory health, their characteristics in the paediatric population are scattered in the literature and not systematized.
Aim: Systematically review the different acoustic RS properties in healthy children and in children with different respiratory disorders. Methods: MEDLINE, EMBASE, AMED and CINHAL databases were searched on Sept 2020. One author extracted data and two independently assessed the quality of the articles using the National Heart Lung and Blood Institute quality assessment tool.
Results: Twenty-eight studies were included with a total 2032 participants (44% with a respiratory condition, such as asthma, bronchiolitis, cystic fibrosis, presence of wheezing and non-specified low respiratory tract infections). A high heterogeneity in the procedures, outcomes and outcome measures used was found. Healthy participants showed lower values of F50 (from 194 ± 26 to 521 ± 18Hz) than those with asthma (from 140 ± 8 to 769 ± 85Hz) or bronchiolitis (from 100 to 80Hz). F50 tend to increase with provocation tests (136 ± 9 to 909 ± 81Hz) and decrease with treatments (128 ± 6 to 781 ± 57Hz). Wheeze rates ranged from 0 to 24.7 ± 25% on asthmatic participants. Crackles findings ranged from 6% on people with recurrent wheezing to 30.8% in middle lobe atelectasis.
Conclusion: RS show different acoustic properties in healthy children vs with different respiratory disorders and thus may be useful in the diagnostic and monitoring on paediatrics.

1. Introduction

Respiratory complaints are about one-quarter of primary care consultations among children [1] and the leading reason for hospitalization in infants after the neonatal period [2,3]. More precisely, lower respiratory tract infections (LRTI) are the number one killer in children under the age of 5 years old [4–7].

Currently, health professionals use their clinical rationale to diagnose respiratory conditions but there is no accurate clinical algorithm to diagnose most respiratory diseases. Chest X-ray is the gold standard for detecting and monitoring respiratory infections [8–10]. However, it has been recommended that it should not be performed routinely in infants due to its limited value for diagnosing and classifying disease severity in uncomplicated situations, associated costs and doses of radiation delivery [11–14]. All these factors prevent the monitoring of paediatric patients with the required frequency.

Respiratory sounds, detected with a stethoscope, are directly related to the movement of air, changes within the lung tissue and position of secretions within the tracheobronchial tree, which make them valuable indicators of respiratory health [15–21]. Additionally, respiratory sounds overcome some of the drawbacks with imaging methods, as stethoscopes are nearly universally available, inexpensive, non-invasive, comfortable, cost-effective, can be repeated as often as necessary and require minimal participant co-operation [15–22].

Research of the acoustic properties of paediatric respiratory sounds has shown that the presence of respiratory diseases is often marked by changes in normal respiratory sounds and the presence of adventitious respiratory sounds (ARS), i.e., crackles and wheezes. This highlights the

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usefulness of respiratory sounds to detect and inform the clinical course of respiratory diseases and treatments. Nevertheless, auscultation presents high levels of interobserver subjectivity [23–26] as it depends not only on the experience but also on the memory, visual/hearing capacities of health professionals, the terminology used and acoustic properties of the stethoscopes [26–31].

Computerized respiratory auscultation may contribute to overcoming these shortcomings [32] as it allows signal amplification and ambient noise reduction [33] and allow respiratory sounds to be analysed, saved, revisited and reanalysed, avoiding memory problems and potential difficulties with transcribing data [25].

Nevertheless, respiratory sounds change according to age, body height, position and presence of respiratory conditions [15,22,26]. There is information published on the respiratory sounds of children however, this knowledge is scattered in the literature, without systematization. Without enhancing our understanding of the acoustic properties of respiratory sounds and the existence of reference values in healthy children, health professionals are limited in interpreting changes in respiratory sounds. In this sense, this study aimed to systematically review the characteristics of computerized respiratory sounds in the paediatric population, with and without lung diseases.

2. Methodology'

This systematic review is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [34] (Appendix A).

2.1. Search strategy

A specific search in the Cochrane Library and the International database of prospectively registered systematic reviews (PROSPERO) was conducted prior to the development of this review to exclude the existence of similar reviews/protocols. Since no similar studies were found, the systematic review protocol was registered at PROSPERO (ref. CRD42016041941).

An electronic literature search was performed in April 2020 in MEDLINE, EMBASE, AMED and CINHAL databases. The search strategy was performed as recommended [35] and the search terms Th e search terms were based on a combination of the following keywords: Paediatric OR paediatric OR new-born OR infant OR toddler OR children OR teenager OR adolescent OR baby (for Population) AND healthy OR lower respiratory tract infection OR bronchiolitis (for Comparisons) AND computerized auscultation OR computerized auscultation OR electronic auscultation OR automatic auscultation AND sound AND lung OR pulmonary OR respiratory OR breath* OR wheeze* OR crackle* OR adventitious (for Outcomes). . Weekly updates have been performed until September 2020. The reference lists of the selected articles were scanned for other potentially eligible studies. Hand literature search was also performed.

2.2. Eligibility criteria

Studies were considered eligible if they were validating, exploring or using computerized respiratory sounds in a paediatric population, i.e., ≤18 years and were written in English, French, Spanish or Portuguese.

Papers were excluded if respiratory sounds were assessed with conventional auscultation only or if studies were conducted on animals. Additionally, book chapters, abstracts in conferences or meetings, single case studies, letters to the editor, commentaries to articles, unpublished work, study protocols or reviews, were excluded.

2.3. Study selection

Initially, duplicated studies were removed. Then, the screening of abstracts, selection of the papers against the inclusion/exclusion criteria and data extraction was performed by one researcher and reviewed by a second researcher. The full text of potentially relevant articles was screened for content to decide on its inclusion. For each accepted study, the following data were extracted to a structured table: study design, author, year and country, participants characteristics, intervention, data collection procedures, recording device, data analysis, outcome measures and findings.

2.4. Quality assessment

Two authors independently assessed the quality of the studies using the National Heart Lung and Blood Institute (NHLBI) quality assessment tool (Appendix B) [36]. This tool assesses the quality of before-after (pre-post) studies with no control group (12 different criteria) and observational cohort and cross-sectional studies (14 different criteria) [36]. Ratings are given to each study for overall quality (i.e., good, fair or poor).

2.5. Data analysis

The inter-rater agreement analysis was performed using Cohen's kappa [37] to determine the consistency of the quality assessment performed by the two reviewers. The value of Cohen's kappa was interpreted as i) <0.00–0.20: none ii) 0.21–0.39: minimal agreement; iii) 0.40–0.59: week; iv) 0.60–0.79: moderate; v) 0.80–0.90: strong; vi) 0.91 to 100: almost perfect agreement [38]. The statistical analysis was performed using SPSS version 24.

3. Results

3.1. Study selection

Database search identified 963 records and the hand search retrieved 17 additional studies. After removal of duplicates, 895 records were screened for relevant content. During the title, abstract and keyword screening, 809 articles were excluded. The full text of the 86 potentially relevant articles was assessed, and 58 articles were excluded due to the following reasons: the sample was not paediatric, or the age range was not stated (n=36); presented conventional auscultation only (n=9); was a book chapter (n=2) or a letter to the editor (n=1), was conducted on animals (n=1) or did not include data on respiratory sounds (n=9). Twenty-eight original articles were included in the review (Fig. 1), as showed in PRISMA's flowchart [39].

3.2. Quality assessment

Seven observational studies had fair (46.6%) [40–45], four had good (26.7%) [46–49] and four had poor (26.7%) [50–53] quality (Table 1). Considering the 12 before-after studies, six had fair (50%) [21,29, 54–57] and six had good [58–63] quality (appendix B). The randomized controlled-trial had good quality [64]. The overall agreement between the two reviewers was almost perfect (85.71%) and kappa revealed a

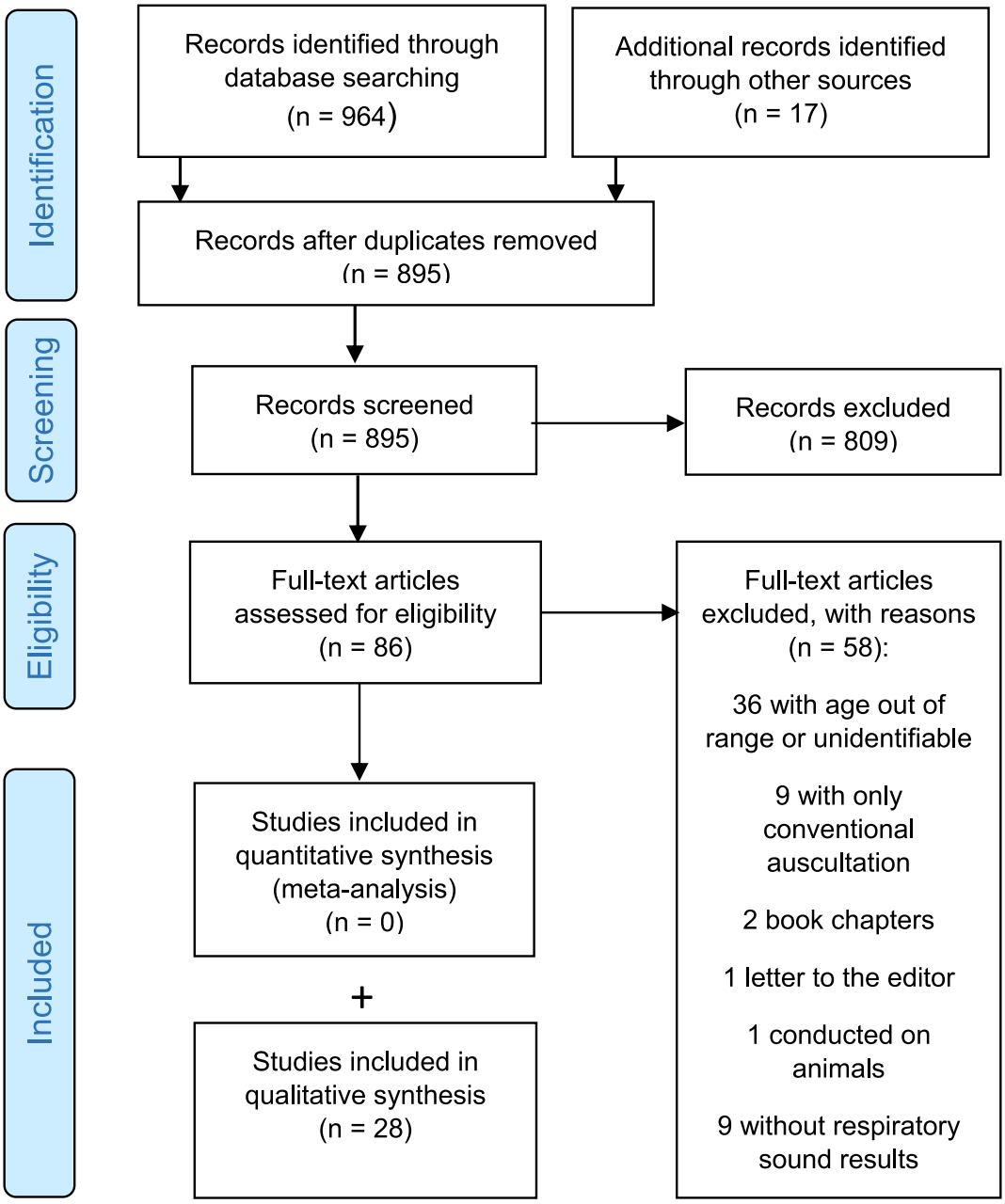

Fig. 1. Flow diagram of the literature search.

Table 1
Computerized respiratory sounds in paediatrics: observational, cohort or cross-sectional studies (n=13).

Author, Year	Country	Participants and intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
Adachi, 2016	Japan	Group 1 (G1): Right middle lobe atelectasis • n= 13: 8 ♀ 5 ♂ • 5 ± 1.4 years Intervention Treatment: • standard RPT (CPAP mask, 3–4 times daily, 50 breaths) • bronchodilator • oxygen therapy if needed Group 2 (G2): Healthy • n=16: 6 ♀ 8 ♂ • 5.6 ± 1.5 years	• Sensors over AS-R, AS-L • Slow and deep breathing (examiner used hand signals to direct the inhalations and exhalations) • Supine position • Recording for 30 s: - G1 at baseline and after the radiographical resolution of atelectasis - G2 at baseline	• Air-coupled microphones • IC recorder (16-bit resolution, sampling frequency of 44.1 kHz)	• FFT (2048 points, Hanning window) • Sound pressure level in three octave bands (100–200 Hz, 200–400 Hz, and 400–800 Hz) • Visual inspection of spectrogram and time-expanded waveform (according to CORSA) for ARS	• Sound pressure level (dB) on 3 different octave band frequency levels (100–200 Hz. 200–400 Hz and 400–800Hz) analysed by R/L I/E phases • Presence of ARS	Baseline • Inspiration phase: 100–200Hz: 80.1 ± 4.4 (G2) vs 77.6 ± 3.8 (G1) p=0.13 200–400Hz: 78.3 ± 4.3 (G2) vs 75.8 ± 4.4 (G1) p=0.15 400–800Hz: 65.9 ± 4.9 (G2) vs 64.1 ± 6.3 (G1) p=0.42 • Expiration phase: 100–200Hz: 74.4 ± 4.7 (G2) vs 72.7 ± 4.4 (G1). p=0.33 200–400Hz: 68.4 ± 5.8 (G2) vs 66.9 ± 5.4 (G1) p=0.50 400–800Hz: 54.2 ± 5.6 (G2) vs 55.3 ± 5.5 (G1) p=0.60 • Inspiratory R/L ratios: 100–200 Hz: 1.0 ± 2.7 (G2) vs −2.2 ± 2.1 (G1) p=0.02 200–400 Hz: −1.4 ± 2.3 (G2) vs −4.8 ± 2.5 (G1) p=0.001 400–800 Hz: −1.7 ± 2.7 (G2) vs −5.9 ± 2.3 (G1) p=0.007 • Expiratory R/L ratios: 100–200 Hz: 1.5 ± 3.2 (G2) vs −0.6 ± 3.3 (G1) p=0.11 200–400 Hz: 2.4 ± 3.2 (G2) vs −0.1 ± 3.9 (G1) p=0.08 400–800 Hz: 0.5 ± 3.0 (G2) vs −1.5 ± 2.3 (G1) p=0.06 • R/L ratios: 100–200 Hz: −6.6 ± 2.0 (G2) vs −4.8 ± 2.1 (G1). p=0.03 200–400 Hz: −11.9 ± 2.9 (G2) vs −9.0 ± 3.6 (G1) p=0.02 400–800 Hz: −13.5 ± 2.6 (G2) vs −9.5 ± 3.7 (G1) p=0.01 After RPT • Inspiratory R/L ratios: (*continued on next page*)

Table 1 (*continued*)

Author, Year	Country	Participants and intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
							100–200 Hz: 1.0 ± 2.7 (G2) vs −1.4 ± 2.2 (G1) p=0.02 200–400 Hz: −1.4 ± 2.3 (G2) vs −3.8 ± 2.7 (G1) p=0.02 400–800 Hz: −1.7 ± 2.7 (G2) vs −5.1 ± 4.4 (G1) p=0.03 • Expiratory R/L ratios: 100–200 Hz: 1.5 ± 3.2 (G2) vs −1.1 ± 3.2 (G1) p=0.06 200–400 Hz: 2.4 ± 3.2 (G2) vs −1.2 ± 2.6 (G1) p=0.003 400–800 Hz: 0.5 ± 3.0 (G2) vs −1.6 ± 3.2 (G1) p=0.008 • R/L ratios: 100–200 Hz: −6.6 ± 2.0 (G2) vs −6.5 ± 3.2 (G1) p=0.91 200–400 Hz: −11.9 ± 2.9 (G2) vs −12.1 ± 2.4 (G1). p=0.84 400–800 Hz: −13.5 ± 2.6 (G2) vs −11.0 ± 3.7 (G1). p=0.06 • ARS (Coarse crackles: n=4 and Ronchi: n=7) disappeared in all participants of the G1
Bokov 2016	France	Presence of 1 abnormal respiratory sound (wheeze, crackle, rhonchus) acute laryngitis or rhinitis: Presence of wheezing: • 14 ♀ 13 ♂ • 8 [4–7](months Absence of wheezing: •22 ♀ 46 ♂ •15 [6–36] months	• Microphone close (5–10 cm) to the mouth and over TR • Breathing without vocals or crying for ≥50% recording length • Recording for 30 s	• Microphone (sensitivity at 94 dB SPL @ 1 kHz is −42 dBV/Pa, frequency response curve presenting less than 0.1% variation in the 100 Hz–4000 Hz zone)	• Sampling frequency: 16 KHz • Segments of length 64 ms with 50% overlap using a Hanning window • WH detection: FFT • Sounds frequency between 200 and 2500 Hz	• WH% • Duration of each WH (ms) • F50 (Hz) • PSD (W/Hz) • Features (F1–F14) of PSD	Presence of wheezing (mouth vs neck) • WH%: 46 ± 31 vs 16 ± 14 • Duration WH: 151 ± 39 vs 95 ± 40 • F50: 399 ± 106 vs 762 ± 271 • PSD: 16.8 ± 5.5 vs 5.6 ± 5.5 Absence of wheezing (mouth vs neck) • WH%: 61 ± 46 vs 22 ± 27 • Duration of each WH: 148 ± 32 vs 90 ± 48 • F50: 396 ± 90 vs 683 ± 253 • PSD: 18.0 ± 6.4 vs 4.3 ± 4.1
Ellington, 2014	Perú	Healthy: • n=151: 71 ♀ 80 ♂		• Digital stethoscope • Standard mp3 recorder	• Sampling frequency at 44.1 kHz	• MFCC • PW (s)	Mean [5 and 95% percentiles]

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Country	Participants and intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
		• 2.2 ± 1.4 years	• Sensors over AS-R, AS-L, PS-R, PS-L, AI-R, AI-L, PI-R, PI-L • Normal breathing pattern without deep breaths • Supine or upright position • Recording for 10 s		• Segments of 2-s using a rectangular window with 50% overlap. • Signals low-pass filtered using a fourth order Butterworth filter at 1 kHz cut-off, down-sampled to 2 kHz, normalized to have zero mean and unit variance. • Power spectrum with FFT (2^{14}-point) and Butterworth filter (at 20 Hz)	• SL (dB/octave) • PLN (dB) • PR (%) • spectral shape (scales) • temporal modulations (rates).	• $MFCC_1$ $p<0.001$: ALL: 4.9 [4.2;5.4] AS-R and L: 4.7 [3.8;5.7] AI-R and L: 4.7 [3.9;5.6] PS-R and L: 5.2 [4.0;6.1] I-R and L: 5.1 [3.7;6.2] • $MFCC_3$ $p<0.001$: ALL: 1.1 [0.8;1.4] AS-R and L: 1.0 [0.6;1.3] AI-R and L: 1.0 [0.7;1.4] PS-R and L: 1.1 [0.7;1.5] I-R and L: 1.1 [0.7;1.5]BR and BL: 1.1 [0.7;1.5] • PW $p<0.001$: ALL: 158.3 [93.4;237.2] AS-R and L: 174.9 [91.2;260.11 AI-R and L: 168.0 [84.5;250.1] PS-R and L: 139.3 [77.9;232.0] I-R and L: 138.1 [71.8;199.8] • $Scales_1$ x IE-3 $p=0.002$: ALL: 94.6 [78.0;110.1] AS-R and L: 99.2 [67.5;119.2] AI-R and L: 95.8 [67.5;119.2] PS-R and L: 90.5 [57.1;123.1] I-R and L: 90.9 [53.6;122.5] • $Rates^{+}_1$ x IE-3 $p=0.002$: ALL: 19.0 [12.7;24.2] AS-R and L: 16.2 [6.9;24.9] AI-R and L: 16.2 [8.3;23.3] PS-R and L: 17.6 [10.1;25.3] I-R and L: 17.7 [10.3;24.9] • $Rates^{-}_1$ x IE-3 $p=0.004$: ALL: 10.9 [7.8;13.5] AS-R and L: 9.0 [4.2;12.7] AI-R and L: 8.9 [5.1;12.2] PS-R and L: 9.8 [6.1;13.7] I-R and L: 9.8 [6.0;13.0]
Faber et al., 2015	Netherland	Bronchiolitis: • n=30: 12 ♀ 18 ♂ • 4.9 ± 4.8 months Intervention Treatment:	• Sensors over TR, AS-R, AS-L, AI-R, AI-L • Recordings for 5 min: - Before/after 15min of treatment	• Acoustic sensors • Pulmotrack Microphone Pneumograph belt sensor	• Karmelsonix software algorithms for WH • Frequency content between 50 and 3.000 Hz	• Presence of wheezing • WH%-Ttot • Breathing frequency (breaths/min) • I/E ratio	Before vs after: • Wheezing: 9 of 27 (33%) increased 5 of 27 (18%) decreased

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Country	Participants and intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
		• Hypertonic (3%) saline solution • volume: 4 ml • via jet nebulizers with continuous flow of 100% oxygen	• Ambient microphone + chest impedance			• No. cough episodes	• WH%-Ttot: 3.4 ± 3.84% vs 2.0 ± 2.7499 p=0.05 • Breathing frequency: 0.70 ± 0.61 vs 0.52 ± 0.70 p=0.23 • I/E: 0.85 ± 0.15 vs 0.85 ± 0.18 p=0.93 • No. cough episodes: 1.44 ± 2.42% vs 2.63 ± 3.36 p=0.03
Gnitecki, 2004	Canada	Non-specified health status: Responders (drop of ≥20% of FEV1 after BPT): • n=4: 3 ♀ 1 ♂ • 11 ± 3 years Non-responders (drop of <20% of FEV1 after BPT): • n=4: 2 ♀ 2 ♂ • 12 ± 2 years Intervention Direct BPT: • methacholine •starting concentration of 0,2 mg/ml doubling concentrations for 2 min until drop of FEV1≥20% (Responders) or when the maximal dose of 8 mg/mL was reached	• Sensor over AI-R • Facemask attached to a pneumotach • Normal breathing • Recordings for 70 s (including a 10 s breath hold at the end of the recording): -Baseline/after BPT	• Accelerometer • Pneumotachograph • Pressure transducer	• Digitization at 10,240 Hz and 12-bits. The flow signal down sampled to 320 Hz • Signals amplified (200x) and filtered with 8th order Butterworth passband of 7.5–2500 Hz • Two fractal dimension (FD) algorithms were applied: Katz (KDF) and Variance (VFD) • True and false positives (TP and FP) between values of sounds and ΔFEV1 • Frequency content between 75 and 600 Hz filtered into 4 ranges (75–600, 75–150, 150–300 and 300–600 Hz) with 5th order Butterworth on MATLAB	• Power (dB): RMS-SNR RMS-SNR + KFD RMS-SNR + VFD	Responders: • RMS-SNR: 58.3 ± 39.3% TP; 26.1 ± 32.8% FP • RMS-SNR + KFD: 90.3 ± 12.6% TP, 23.4 ± 38.2% FP • RMW-SNR + VDF: 63.5 ± 43% TP, 24.9 ± 43.8% FP Non-responders: • RMS-SNR: 60.2 ± 10.0% TP; 45.4 ± 15.4% FP • RMS-SNR + KFD: 79.9 ± 12.8 %TP, 28.1 ± 26.5% FP • RMW-SNR + VDF: 72.2 ± 4.8% TP, 44.5 ± 21.0 FP
Hidalgo, 1991	United States of America	Healthy: • n=35: 17 ♀ 18 ♂ • Age range: 0–13 years	• Microphone over AS-R (0.7 cm distance) • Normal breathing • Standing position	• Handheld microphone • Preamplifier with filter • Magnetic-tape recorder	• 4096 samples /s and low-Pass filter at 2000 Hz • Sound preamplified (x5000) and high pass filter (5-pole elliptical filter, cut-off frequency 100 Hz, minimum stop-band loss of 60 dB at 50 Hz) • FFT (4096 points with 1 Hz) Amplitude frequency from 100 to 1000 Hz	Inspiratory amplitude frequency spectra (IAFS) with •F25 (Hz) • F50 (Hz) • F75 (Hz) • F95 (Hz)	• F25=139 ± 15 /136 • F50=194 ± 26 • F75 = 277 ± 34 • F95= 467 ± 45 • Different shapes in children's vs adult's IAFS pattern on F25, F50 and F95 p<0.05 but not on F75 p = 0.11 • Decrease in F25, F50. and F75 associated with increasing age or height in children p<0.001 • No relationship of F95 with age or height p > 0.05
Kevat, 2017	Australia	Cystic fibrosis, LRTI, asthma or pre-school wheeze: • n=20: 4 ♀ 16 ♂ • 7.6 years (4.6–17.1)	• Auscultation on PS-R, PS-L, PI-R, PI-L. Recording for 20 s (each quadrant)	• 2 different digital stethoscopes	• High-pass filter (Butterworth, 100 Hz. 6th order) and a low-pass filter (Butterworth, 1000 Hz. 4th order) • Spectrograms analysed and listened by paediatric respiratory doctor	WH: • dominant frequency (Hz) • I/E ratio •duration (ms) CR: • duration (s)	• Total of 156 recordings WH: • periodic waveform with dominant frequency range of 100–1050 • i/e ratio: 1/3

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Country	Participants and intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
							• expiratory longer (0.29 (0.03–1.2)) than inspiratory (0.19 (0.04–0.4)) CR: • duration 10–15 ms (range 6–20 ms)
Mazic, 2003	Croatia	Asthma: • n=7 (gender not reported) • 3–7 years	• Sensor on TR, AI-R, AI-L • Normal (NB) or forced breathing (FB) • Supine position	• Microphone • Accelerometers	• Sampling with amplitude-frequency characteristic within ±5 dB and frequency range from 100 Hz to 2 kHz and at 8 kHz rate. • Signals analysed with MATLAB v6 • Visual and auditory inspection of the recorded signals.	• WPF (Hz) • Duration WH (ms) • No. WH • No. WH in 10 s	*Mean [min; max]* • NB (n=1): WPF = 400 Duration WH = 100 No. WH = 1 No. WH in 10 s: 4 • FB (n=4): WPF = 352.5 ± 82.3 [250;460] Duration WH= 200.0 ± 93.5 [100;350] No. WH = 1.3 ± 0.4 [1,2] No. WH in 10 s: 3.24 ± 1.3 [1,4] • NB + FB (n=2): WPF = 380.0 ± 0.0 Duration WH= 250.0 ± 0.0 No. WH = 2.5 ± 0.5 [2,3] No. WH in 10 s: 3.0 ± 1.0 [1,4]
Murayama, 2019	Japan	Healthy in the past 7 days: • n=283: 147 ♀ 136 ♂ • 7 (7–9) months Acute respiratory infection (ARI) in the past 7 days: • n=115: 61 ♀ 54 ♂ • 9 (7–18) months	• Handheld microphone over AS-R • Normal breathing • Standing position • Recordings for ≥10 s	• Microphone • Pneumotachograph • Sound spectrometer (10,240 Hz)	• Sampling frequency at 10,240 Hz Frequency read digitally at 10 Hz intervals Band-pass filter from 40 to 2500 Hz Spectra obtained with Hanning window • FFT • Hanning window • Frequency content between 100 and 2500 Hz	• Presence of WH • F99 (Hz) • spectrum curve indices: - Spectral slope at 600–1200 Hz (-dBm/octave) - A3/AT (%) B4/AT (%) • RPF50 (dBm/Hz) • RPF75 (dBm/Hz)	Presence of WH: • Healthy: n=3: 2 ♀ 1 ♂; 7 (5–7) months • ARI: n=10: 5 ♀ 5 ♂; 14 (7–18) months No differences on other outcome measures between the group with and without wheezes.
Pasterkamp, 1996	Canada	• Healthy infants: • n=10: 5 ♀ 5 ♂ • 1 ± 0.5 days • Healthy children: • n=9: 5 ♀ 4 ♂ • 7 ± 0.8 years	• Sensor over PI-R • Mask covering mouth and nose or nose clip + mouth piece • Infants at LF of 15 ml/s/kg ± 20% tolerance and children at both LF and HF of 30 ml/s/kg ± 20% tolerance only • Sleeping in the prone position • Recordings for 60 s	• Sound sensor • Pneumotachograph • Differential pressure transducer • Video tape • Sound digitalizer	• 10,240 samples/s with 12 bits resolution • Length of recordings: • Infant: 52.7 ± 9.3 at LF • Children: 46.1 ± 8.2 at LF, 39.2 ± 7.8 at HF • Segments containing artifacts were identified visually and by auditory verification and excluded • Low-pass filtered (sixth order Butterworth, cut-off at 2400 Hz) • The sound signal was parsed into segments of 2048 data points with a 50% overlap of points between successive segments windowed with a Hanning function before power spectral estimates were obtained by FFT • Sample frequency between 100 and 2000 Hz	• Length of digitized recording per subject (s) • Fmax (Hz) • Fmin (Hz) • Ti/Ttot (%) • Average flow at inspiration (FLow-i) and expiration (Flow-e) (L/s) • Signal to noise ratio • Fmax spectral slope (at LF and HF)	• Ti/Ttot: Gain in power at HF: Inspiratory signal-to-noise ratio: • Infant: 0.41 ± 0.03 at LF • Children: 0.38 ± 0.03 at LF, 0.42 ± 0.06 at HF • FLow-i: • Infant: 0.05 ± 0.01 at LF • Children: 0.38 ± 0.07 at LF, 0.71 ± 0.12 at HF • FLow-e: • Infant: 0.03 ± 0.01 at LF • Children: 0.37 ± 0.07 at LF, 0.73 ± 0.16 at HF • Fmin:

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Table 1 (*continued*)

				• Average respiratory sound spectra obtained at LF and at HF	• Spectral slope at 300–700 Hz (dB) • Gain in power at 20–100 Hz (dB)	Infant: 126 ± 36 at LF Children: 57 ± 38 at LF (F probability = 0.016: p<0.001) • Children at HF: 1270 at HF • Fmax: Infants had higher quartile frequencies and spectral edge frequencies than children at LF (F probability <0.01). • Children had higher Fmax as well as a higher SE 95 and SE99 with HF p <0.05 at HF • Spectral slope: • Infant: −17.7 ± 3.9 • Children: −17.2 ± 1.7 • Gain in power: • Infant: 8.0 ± 4.1 • Children: 9.2 ± 2.6
Ramanathan,.2020	Australia	Term infants (between 37 and 40 weeks) without pulmonary pathology or major foetal deformation, non instrumental delivery and no required resuscitation at birth. Group CS: Delivered via elective caesarean section • n=39: 24 ♀ 15 ♂ • 38 [37,39] gestation weeks • 3222 ± 0.297 Kg • 1-min Apgar score: 9 [8,9] Group NVD: Normal vaginal delivery • n=32: 17 ♀ 15 ♂ • 3166 ± 0.447 Kg • 1-min Apgar score: 9 [9,9]	• Auscultation over anterior and posterior right chest. • Non-crying segments • Supine position for posterior recording; Prone to anterior recording • Average of the anterior and posterior recordings for each infant at each time point • Recording for 60 s: - 1 min post-delivery -2 h post-delivery	• Digital Stethoscope • Standard audio recording application on a smartphone	• Signals analysed with MATLAB R2018a • A fourth order Butterworth band pass filter at 100–1000 Hz • FFT (2048 points, Hanning window) • Sound pressure level in three octave bands (Low:100–200 Hz, Medium: 200–400 Hz, and High: 400–800 Hz) • Visual inspection of spectrogram and time-expanded waveform (according to CORSA) for ARS • Sample frequency between 100 and 1000 Hz	• Mean frequency (Hz) • F25 (Hz) • F50 (Hz) • F75 (Hz) • AP (x10^{-2}n.u.) • Power ratios within frequency bands: Low (100–200 Hz (LBF), medium 200–400 Hz (MBF), high 400–800 Hz (HB).	1 min vs 2 h • Mean frequency Combined: 334 ± 35 vs 303 ± 47 (p=0.0002) NVD: 346 ± 40 vs 304 ± 44 (p=0.0003) • F25 Combined: 214 [182;244] vs 176 [153;201] (p<0.0001) NVD: 234 ± 57 vs 184 ± 45 (p=0.0004) • F50 Combined: 314 ± 50 vs 24 ± 65 (p=0.009) NVD: 329 ± 57 vs 281 ± 66 (p=0.001) • F75 Combined: 416 [396;457] vs 396 [353;440] (p=0.01) NVD: 430 ± 46 vs 392 ± 67 (p=0,01) • AP Combined: 2.49 [1.64;4.38] vs 0.74 [0.43;1.79] (p<0.0001) NVD: 2.50 [1.47;4.38] vs 0.63 [0.40;1.60] (p=0.016) CS: 2.49 [1.91;4.65)] vs 0.77 [0.53,2.28] (p=0.0002) • LBF Combined: 0.27 ± 0.11 vs 0.37 ± 0.15 (p=0.0001) NVD: 0.23 [0.15;0.31] vs 0.38 [0.28;0.50] (p=0.0003) CS: 0.29 ± 0.09 vs 0.36 ± 0.14 (p=0.05) • MBF Combined:0.48 [0.39;0.56] vs 0.38 [0.29;0.48] (p=0.003) NVD: 0.48 [0.37,0.57] vs 0.35 [0.28;0.42] (p=0.05) CS 0.48 ± 0.10 vs 0.40 ± 0.11 (p=0.01) • HBF

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Table 1 (*continued*)

							NVD: 0.32 [0.25;0.39] vs 0.28 [0.21;0.36] (p=0.02) NVD vs CS at 1 min • Mean frequency: NVC > CS (p=0.005) • F25: NVD > CS (p=0.01) • F50: NVC > CS (p=0.03) • LBF: NVD < CS (p=0.04) NVD vs CS at 2h • none
Rietveld, 1999	Netherlands	Asthma • n=60: 50 with asthma and 10 without (no gender specified) • 12.1 ± 2.9 years	• Sensor over TR • Continuous respiratory telemetry (transmitter and battery in a waist belt and at night. kept in a bag beside the pillow) • Recordings for 20 s	• Microphone (range 20–25000 Hz within 3 dB) • Small transmitter • Receiver • Hifi video recorder	• Samples of 2 s duration each prefiltered by a fourth-order Butterworth analogue filter with a band pass of 100–1500 Hz and subsequently processed with a 1300 Hz low-pass digital filter • Sample frequency between 100 and 1300 Hz divided in 26 bands of approximately 46 Hz each. • FFT Categorization by human examiners and by artificial neural networks	• Presence of WH	• Presence of WH: • in 11 with a decrease in PEF ≥20%. • in 4 a decrease in PEF<20% • in none when there was no PEF decrease. • Of the 34-h associated with more than 20% decrease in PEF. wheezes were observed in 31 (91%) and in 4 of the hours associated with a decrease in PEF of less than 20% (0.7%).
Sánchez, 2005	Canada	Acute bronchiolitis (16 with RSV): • n=22: 8 ♀ 14 ♂ • 5.2 ± 1 months Intervention Treatment: •10 min of oxygen nebulization with salbutamol (0.5 mL solution, 5% concentration).	• Sensors over PI-R, PI-L • Airflow at 0.1 ± 0.02 L/s, silicone air-cushioned covering mouth and nose • Participant sleeping in a prone position • Recordings for 2 min: - Baseline - After 20 min of salbutamol administration	• Two sound sensors (flat frequency response from 60 to 500 Hz, a small gain of approximately 4 dB between 500 and 1000 Hz, and a −15 dB/octave roll-off above 1200 Hz) • Infant mask • Pneumotachograph • Differential pressure transducer • Analog-to-digital converser	• Low-pass filtered (sixth order Butterworth, cut-off at 2400 Hz) • Segments of 2048 data points with a 50% overlap of points between successive segments and windowed with a Hanning function. • FFT Distinctive peaks on frequency Periodic waveform Auditory verification on playback • Frequency content between 100 and 1000Hz	• WH%-Ttot • Type of wheezing: sinusoidal (SW) complex (CW). • avgFw (Hz) • Minimal frequency (Hz) • Duration of segments (ms) • For inspiration and expiration: F25 (Hz) F50 (Hz) F75 (Hz) F99 (Hz)	• Range between 100 and 800 Hz • 11 participants (50%) with SW + 11 with CW • Minimal frequency higher in SW (252 ± 10) than in CW (162 ± 16) p<0.001 • Duration of segments longer in SW (250 ± 22) than in CW (35 ± 11) p<0.001 • Harmonics and sinusoidal waveforms in all SW vs only 2 in CW p<0.001 • Positive salbutamol response: Correlation between WH%-Ttot on SW (9/11) vs CW (3/11) p<0.01 Increase F25 and F50) after salbutamol p<0.01 Positive linear correlation between WH%-Ttot with F50 and F99 p<0.001 Correlation between salbutamol and increase of F25 and F50 p<0.01
Shioya, 2019	Japan	Acute respiratory infection (within past 7 days): • n=115 (gender not specified) • 3–24 months Healthy: • n=283: 136 ♀ 147 ♂	• Microphone (handheld) over AS-R • Normal breathing • Standing position • Recordings for ≥10 s	• Microphone • Amplifying unit for 100–2500 Hz sounds • Sound spectrometer	• Sampling frequency was 10,240 Hz and the spectra were obtained using a Hanning window • FFT • Sample frequency between 100 and 1000 Hz	• F99 (Hz) • spectrum curve indices: - Spectral slope (-dBm/octave) - A3/AT (%) • RPF50 (dBm/Hz)	**Healthy with:** (median [range]) With presence of wheezing vs not • A3/AT: 12.7 [5.4, 19.9] vs 12.4 [7.0, 20.1]

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Table 1 (*continued*)

• 9.0 ± 4.5 months	• RPF75 (dBm/Hz)	• RPF75: 6.9 [1.8, 17.0] vs 6.6 [2.5, 18.0] • RPF50: 6.7 [2.1, 14.3] vs 6.3 [2.3, 18.7] • Slope: 26.3 [3.1, 57.9] vs 27.7 [-1.7, 66.5] • F99: 690 [260, 1260] vs 675 [280, 1460] Past RSV vs not • A3/AT: 12.4 [7.2, 20.1] vs 12.5 [5.4, 19.9] • RPF75: 6.4 [3.4, 14.2] vs 6.6 [1.8, 18.0] • RPF50: 7.1 [3.0, 11.2] vs 6.4 [2.1, 18.7] • Slope: 27.0 [14.5, 54.5] vs 27.1 [-1.7, 66.5] • F99: 900 [400, 1340] vs 670 [260, 1460] p=0.024 Past hospitalization vs not • A3/AT: 11.1 [7.2, 12.0] vs 12.6 [5.4, 20.1] p=0.042 • RPF75: 5.8 [5.6, 7.4] vs 6.7 [1.8, 18.0] • RPF50: 6.8 [5.1, 7.7] vs 6.4 [2.1, 18.7] • Slope: 27.0 [19.6, 33.8] vs 27.1 [-1.7, 66.5] • F99: 815 [370, 1260] vs 680 [260, 1460] With allergy vs not • A3/AT: 12.1 [9.9, 16.7] vs 12.5 [5.4, 20.1] • RPF75: 8.0 [4.3, 14.1] vs 6.5 [1.8, 18.0] p=0.008 • RPF50: 7.7 [4.1, 12.9] vs 6.3 [2.1, 18.7] p=0.004 • Slope: 31.5 [20.9, 64.9] vs 26.7 [-1.7, 66.5] p=0.013 • F99: 720 [380, 970] vs 680 [260, 1460] With atopic dermatitis vs not • A3/AT: 12.3 [8.0, 17.0] vs 12.6 [5.4, 20.1] • RPF75: 8.0 [3.4, 18.0] vs 6.5 [1.8, 17.4] p=0.021 • RPF50: 7.6 [3.2, 16.5] vs 6.2 [2.1, 18.7] p=0.001 • Slope: 30.8 [3.9, 66.5] vs 26.7 [-1.7, 66.4] • F99: 730 [350, 1130] vs 670 [260, 1460] p=0.033 With family history vs not

(*continued on next page*)

Table 1 (*continued*)

							• A3/AT: 12.7 [7.0, 20.1] vs 11.9 [5.4, 19.0] p=0.037 • RPF75: 6.9 [2.5, 18.0] vs 6.3 [1.8, 16.8] • RPF50: 6.4 [2.1, 16.2] vs 6.4 [2.3, 18.7] • Slope: 27.0 [-1.7, 66.5] vs 27.2 [-1.7, 66.4] • F99: 700 [280, 1340] vs 640 [260, 1460] **Acute respiratory infection (within past 7 days):** (median) • A3/AT: [11.1, 12.7] • RPF75: [5.8, 8.0] • RPF50: [6.2, 7.7] • Slope: [26.3, 13.5] F99: [640, 900]
Tinkelman, 1991	United States of America	Absence of ARS: • n=50 (gender not specified) • 2–6 years Wheezing: • n=18 (gender not specified) • 2–6 years Wheezing and asthmatic: • n=10(gender not specified) • 8–54 years	• Digital stethoscope PI-R • Measures for lung sounds (over PI-R), heart sounds (over precordium) and voice (over PI-R with children singing "ABC") • Normal breathing • Recordings for 40 s	• Digital stethoscope (High Filter Frequency between 20 and 2000Hz) • Phono pneumograph	• Sound segments between 5 and 8 s • Spatial averaging of the points was determined • Frequency content between 60 and 300 Hz	• EV	EV Lung sounds: • No ARS:461 ± 114 2 years old: 476 ± 88 3 years old: 459 ± 119 4 years old: 451 ± 120 5 years old: 468 ± 140 6 years old: 450 ± 93 • Wheezing: 1867 ± 1006 • Wheezing and asthmatic: 1811 ± 1125 Difference between intensity in normal and wheezing children p<0.002

substantial agreement (k=0.79; 95% CI, 0.59 to 0.98; p<0.005).

3.3. Study characteristics

Detail description of the included studies is presented in Tables 1–3.

Studies were published between 1985 and 2020 with 77.7% (n=21) [40–43,46–49,51,53–55,58–66] being published after the CORSA guidelines publication in 2000. Study designs were observational (n=16) (Table 1) and before-after intervention with no control group (n=12) (Table 2). Four observational studies collected and analysed respiratory sounds before and after routine intervention [43,47,48,64]. A total of 2042 participants (840 girls (41.1%); 911 boys (44.6%); in 291 gender was not specified (14.3%)), with an age-range between 0 and 18 years old were included in the studies. A total of 1143 participants where healthy and 899 (44.0%) presented respiratory conditions, i.e., 465 (22.9%) had asthma [29,45,51,54,59,62,67], 286 (14.4%) bronchiolitis [47,64] and 148 (7.3%) other respiratory diseases, such as atelectasis and cystic fibrosis [46,53,66].

Sixteen studies (57,1% of the total sample) described interventions, with provocation tests [29,43,55,56,61,62,67], pharmacological treatments (β2-agonist, oxygen therapy, hypertonic saline solution, epinephrine and fluticasone) [40,47,48,54,57–59,63,68] and physiotherapy treatments [29,55,61,64,67,69].

3.4. Respiratory sound acquisition

Respiratory sounds were mostly recorded during normal breathing [41–44,46,49–52,55,58–61,64,66]. However, forced breathing [51] and slow and deep breathing were also used [40] and seven studies [29,45,48,53,54,57,70] did not report the breathing manoeuvre used during the respiratory sounds recordings. Six studies controlled the ventilation flow at values of approximately 0.1 l/s in infants [47,63] to 0.4–2 l/s in children from 4 to 14 years old [56,62,67,71]. Digital stethoscopes were used in five studies [42,49,50,54,55], accelerometers or piezoelectric sensors in six studies [21,29,43,56,62,63] and microphones in fifteen studies [40,41,44–48,52,53,57,59–61,66,68] to acquire respiratory sounds. Two studies used both accelerometers and microphones [51,64]. Duration of the recordings varied between 10 s [42,46,55,57,60,61,66] and 5 min [48,64], with reported sampling segments for analysis ranging from 64 ms [41] to 8 s [50]. Sixteen studies recorded respiratory sounds at anterior superior right chest [29,40,42,46,48,52,54,55,57–62,66,67], eight at trachea [29,41,45,48,51,56,62,67], eight at anterior inferior right chest [42,43,48,51,56,63,64,67], six at anterior and inferior left chest [42,48,51,63,64,67], four at anterior and superior left chest [40,42,48,67], six at posterior and inferior right chest [42,44,47,50,53,67], three at posterior and superior left and right chest and posterior inferior left chest [42,53,57], one at the left and right axilla [64], one at non specified anterior right and left chest [49] and 1 near the mouth [41]. A substantial methodological heterogeneity was observed throughout the studies.

3.5. Respiratory sound analysis

Respiratory sounds were filtered using Fast Fourier Transformation (FFT) in 23 studies [29,40,41,44–47,49,52,54–57,59,60,62–64,66–68,72,73]. Frequency contents between 40 Hz [54,55,59–61,66,68] and 3000 Hz [29] were used during data analysis. Most studies (n=24) found energy of respiratory sounds between 100 Hz [40,44–47,49,51–53,56,59,62,63,67,68] and 2500 Hz [41,54,55,58–61,66,68].

Legend: Data are presented as mean ± standard deviation or median [interquartile range], unless otherwise stated; ♀-female; ♂-male; A3-third area under the curve; AI - anterior inferior; AM-anterior middle; ARS-adventitious respiratory sounds; AS - anterior superior; AT-total area under the curve of 100 Hz to the highest frequency of the of the of the dBm power spectrum; avgFw-average peak frequency; AX-axilla; BPT-bronchial provocation test; CG-control group; CORSA-computerized respiratory sounds analysis; CR-crackle; EV – energy values as an arbitrary value which correlates with loudness; F25, F50, F75, F90, F95, F99 - frequencies of 25, 50, 75, 90, 95, 99% respectively of the spectral sound measured (Hz); FD-fractal dimension; FEV1-forced expiratory volume on the 1st second; FFT-Fast Fourier transformation; Fmax-maximal frequency; Fmin-minimal frequency; HF-high flow; I-inferior; I/E – inspiratory/expiratory; IC-Integrated Circuit AKA Digital voice; IG-intervention group; L-left; LF – low flow; MFCC-mel-frequency cepstral coefficient (measures chest formation); PEF-peak expiratory flow; PI-posterior inferior; PLN-power of regression line; PR-power ratio; PS-posterior superior; PSD–Power spectral density; PW-spectrum peak width; R/L-right to left; RMS-root mean square of the sound signal; RPF50 or 75-ratio power/frequency at 50 or 75% of the highest frequency of the dBm power (dBm/Hz); RPT-respiratory physical therapy; R-right; RSV-respiratory syncytial virus;; SNR-signal to noise ratio; Te-expiratory time; Ti-inspiratory time; TR-trachea; Ttot-total respiratory time; WH%-wheeze occupation rate; WH-wheeze; WPF-wheezing pitch frequency.

Legend: Data are presented as mean ± standard deviation or median [interquartile range], unless otherwise stated; ♀-female; ♂-male; AI - anterior inferior; AX-axilla; CR-crackle; FFT-Fast Fourier transformation; L-left; R-right; WH%-wheeze occupation rate; WH-wheeze.

3.6. Data synthesis and analysis

Pooling the results was not possible due to the large heterogeneity of the outcomes, outcome measures and procedures used for respiratory sounds recordings and analysis. Instead, a synthesis of all results (Appendix C) per NRS and ARS characteristics was conducted.

3.7. Normal respiratory sounds

Normal respiratory sound characteristics were evaluated in healthy participants [44,46,49,52,62,66,67], children with asthma [54,56,59–62,67,68], bronchiolitis [47] and LRTI, 7 days after the onset [46,66].

The most used outcome measure was median frequency of the spectral sound (F50), measured in Hz (Fig. 2) [41,46,47,49,50,52,54,56,58,60,62,67], followed by frequency at 99% of the spectral sound (F99) [46,58–62,66], the spectral slope [44,46,58–61,66] and the ratio power/frequency at 50% (RFP50) or 75% (RPF75) of the highest frequency of the dBm power [46,58–61,66]. The power of spectral slope showed a

Table 2
Computerized respiratory sounds in paediatrics: before-after (pre-post) studies without control group (n=12).

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
Enseki, 2019	Japan	Asthma: • n=9: 4 ♀ 5 ♂ • 7.0 years	Treatment (bronchodilation): • 1 time • β2 agonist • procaterol 30 μg + saline 2.0 ml	• Handheld microphone over AS-R • Normal breathing • Standing position • Recordings for ≥10 s: - Baseline - After Treatment (15 min)	• Microphone • Pneumotachograph • Sound spectrometer (10,240 hz)	• Sampling frequency at 10,240 Hz Frequency read digitally at 10 Hz intervals Band-pass filter from 40 to 2500 Hz Spectra obtained with Hanning window • FFT • Hanning window • Frequency content between 100 and 2500 Hz	• F99 (Hz) • F50 (Hz) • spectrum curve indices: - Spectral slope at 600–1200 Hz (-dBm/octave) - P3/PT (%) - P4/PT (%) • RPF50 (dBm/Hz) • RPF75 (dBm/Hz)	Baseline vs After Treatment: (median [range]) • F99: 950 [380, 1310] vs 1080 [620, 1290] p=0.02 • F50: 140 [110, 170] vs 160 [120, 190] p=0.061 • Slope: 23.4 [14.8, 31.5] vs 28.5 [19.7, 29.2] p=0.057 • P3/PT: 49.8 [8.8, 76.6] vs 55.2 [11.9, 89.8] p=0.021 • P4/PT: 38.4 [3.7, 60.9) vs 43.0 [2.8, 72.1] p=0.015 • RPF50: 6.0 [2.3, 8.1] vs 6.9 [4.9, 9.2] p=0.011 • RPF75: 4.2 [3.1, —] vs 7.3 [6.7, 8.2] p=0.024
Fenton, 1985	Canada	IG: • Asthmatic with BPT • n=5 (gender not reported) • 10–16 years CG: • Healthy • n=2 • 10 and 19 years	Indirect BPT: • 10 min • exercise testing - bicycle ergometer • increase heart rate to 80% of predicted maximum Bronchodilatation: • salbutamol • 2 times • 200 μg	• Sensors over TR and AS-R • Sitting position • Recording for 3 min: - At baseline. - After BPT - At maximum obstruction - 20 min after bronchodilator Flow measured with pneumotachograph + differential pressure transducer	• Contact accelerometers (frequency responses within ±5 dB over the frequency range 20–2000 Hz) • Pneumotachograph • Tape recorder at 39 cm/s	• Before digital conversion sounds through fifth-order elliptic low-pass filter with a cut-off frequency of 1000 Hz. • Analog-to-digital conversion to sample the sound signals at 2.56 kHz and the flow signal at 10 Hz. • FFT and a 5% cosine data window.	• WH%-Ti • WH%-Te • Max WH frequency (Hz) • WH amplitude ratio (%)	IG Baseline (n=5): WH%-Ti=0.4 ± 0.8 [0;2] WH%-Te=0 ± 0 Maximum obstruction (n=7): WH%-Ti=24.7 ± 25.9 [0;73] WH%-Te=21.6 ± 25.3 [0; 61] After bronchodilator (n=6): WH %-Ti=0 ± 0 WH%-Te=0.4 ± 0.8 [0; 2] Max WH frequency: Inspiration: 630 ± 80 Expiration: 630 ± 110 WH amplitude ratio:

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
						• Frequency content between 110 and 1200 Hz.		29.7 ± 15.7 CG WH%-Ti=0 ± 0 WH%-Te=0 ± 0
Habukawa, 2009	Japan	Asthma All (IG + CG): • n=131: 78 ♀ 53 ♂ • 9.3 ± 2.7 years • Severity (GINA) groups: ✓ 1: 24 intermittent ✓ 2: 56 mildly persistent ✓ 3: 45 moderately persistent ✓ 4: 6 severely persistent IG (included above): • n=69 (age and gender not reported) • Severity (GINA) groups: ✓ 2: 18 mildly persistent ✓ 3: 45 moderately persistent ✓ 4: 6 severely persistent	Treatment: • Fluticasone for 1 month • 100 or 200 mg/day	• Sensor over AS-R • Recording for 10 s: - At baseline for IG + CG - After treatment for IG	• Digital stethoscope • LSA-2000 sound spectrometer • Digital stethoscope signal conditioning unit	• Frequency read digitally at 10 Hz intervals • Band-pass filter from 40 to 2500 Hz • FFT (HF that exceeded −25 dBm in each breath cycle was identified)	• HFI (Hz) • HFE (Hz)	Baseline (IG + CG): • HFI = 666 ± 131 • HFE = 499 ± 115 • Significant correlation between the severity of asthma and HFI p<0.001: Group 1: 576 ± 78 Group 2: 630 ± 137 Group 3: 710 ± 127 Group 4: 769 ± 85 After treatment (IG): HFI decreased from 711 ± 120 before treatment to 565 ± 15 after inhaled corticosteroids' treatment p< 0.001
Habukawa, 2010	Japan	Asthma: • n=17 (age and gender not reported) With wheezing: • n=4 (age and gender not reported) Without asthmatic symptoms: • n=15 (age and gender not reported) All 36 participants: • 14 ♀ 22 ♂	Direct BPT: • methacholine • inhalation 2 ml • starting concentration of 49 μg/ml • doubling concentrations for 1 min until respiratory resistance doubles Bronchodilatation: •salbutamol	• Sensor over AS-R • Normal breathing • Sitting position • Recordings ≥10 s: - Baseline - After BPT	• Digital stethoscope • Signal conditioning unit • Sound spectrometer	• Sound conditioning unit with a 40–2500 Hz band-pass filter and the capacity to analyse sounds from 40 to 2000 Hz • FFT • Spectrograph • HFI and HFE determined manually.	• HFI (Hz) • HFE (Hz)	For all 36 participants: • Max HFI mean (615 ± 220) greater than baseline-HFI mean (482 ± 130) p<0.001 • Post-HFI mean (504 ± 178) lower than Max-HFIp<0.001 • Max-HFE mean (346 ± 96) greater than baseline-HFE mean (290 ± 55) p<0.001 • After BPT- HFE mean (289 ± 76) lower than Max-HFE p<0.001

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
Kondo, 2018	Japan	8.2 ± 3.7 years Asthma: • n=61: 22 ♀ 39 ♂ • 9.2 ± 2.8 years	Treatment (bronchodilation): • 1 time • β2 agonist • procaterol 30 μg + saline 2.0 ml	• Handheld microphone over AS-R • Normal breathing • Standing position • Recordings for ≥10 s: - Baseline - After treatment (15min)	• Microphone • Pneumotachograph • Sound spectrometer (10,240 hz)	• Sampling frequency at 10,240 Hz • Frequency read digitally at 10 Hz intervals Band-pass filter from 40 to 2500 Hz Spectra obtained with Hanning window • FFT • Hanning window Frequency content between 100 and 2500 Hz	• F99 (Hz) • Spectrum curve indices: - A3/AT (%) - B4/AT (%) • RPF50 (dBm/Hz) • RPF75 (dBm/Hz)	Baseline vs After Treatment: • F99: 931.6 ± 268.0 vs 970.1 ± 201.3 • A3/AT: 12.1 ± 1.7 vs 13.6 ± 1.5 p<0.001 • B4/AT: 7.16 ± 1.3 vs 8.12 ± 1.2 p<0.001 • RPF50: 60 ± 1.7 vs 7.47 ± 1.8) p<0.001 • RPF75: 5.80 ± 1.3 vs 7.00 ± 1.4 p<0.001
Malmberg, 1994	Finland	Asthma: histamine BPT responders (decrease FEV1>15%): • n=7: 6♀ 1♂ • 12 (10–14) years histamine BPT non-responders (decrease of FEV1 >15%): • n=4: 2♀ 2♂ • 12 (10–13) years	Direct BPT: • histamine • increasing doses (0.025, 0.1, 0.4 and 1.6 mg) • at intervals of 5 min until drop of FEV1≥15% (responders) or until the maximum dose of histamine was inhaled Bronchodilatation: • salbutamol • 200 μg	• Sensors over TR and AI-R • Flow at 1–1.25 l/s • Sitting position • Recordings for consecutive 30 s (at least 10 respiratory cycles): - Baseline - After BPT (90 s after) - After SALB (15min after salbutamol) • Inspiratory and expiratory peak flows constant. within the range of 1.0–1.25 l/s; all participants were carefully trained	• Air-coupled condenser microphone • Piezoelectric contact sensor • Pneumotachograph • 8-channel data recorder • Analog-to-digital convertor	• Sampling rate at 12 KHz • Signal divided into inspiratory and expiratory phases • Prefilter with 3rd order high- pass filter with a cut-off frequency of 50 Hz. • High-pass filtered (digital Kaiser-FIR filtering) with a cut-off frequency of 100 Hz (24 dB/oct.) • Power spectrum of each respiratory phase was computed using the overlapped- segment method of Welch based on 2048-point FFT with Hanning window • WH detection: evaluated during chest and trachea auscultation + visual examination of a sinusoidal waveform with a duration of more than 200 ms	• F50 within 75–2.000 Hz (Hz) • ΔF50i: difference on inspiration (Hz) • ΔF50e: difference on expiration (Hz) • ΔRMSi: difference on inspiration (Hz) (mV) • ΔRMSe: difference on expiration (Hz). (mV) • range sounds (Hz) for WH and their harmonics	**Chest:** F50 Baseline • Inspiration: responders 177 ± 15; non-responders 164 ± 14 • Expiration: responders 140 ± 8; non-responders 139 ± 16 F50 After BPT • Inspiration: responders 194 ± 17; non-responders 163 ± 12 • Expiration: responders 162 ± 12; non-responders 136 ± 9 F50 After SALB • Inspiration: responders 181 ± 18; non-responders 169 ± 27 • Expiration: responders 136 ± 8; non-responders 128 ± 6 • ΔF50i on responders: After BPT-Baseline = −0.332 ± 0.109 p=0.052 After bronchodilator-Baseline: p<0,05 • ΔF50e on responders: After BPT-Baseline = −0.706 ± 0.085 p=0.001 After bronchodilator-Baseline: p<0,01 • ΔRMSi on responders: After BPT-Baseline = −0.601 ± 0.354 p=0.01 After bronchodilator-Baseline: p<0,01 •ΔFEV1 vs ΔF50: r= 0.865 β = -0.706; p= 0.0001

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
								• responders=> increase of 8% in F50 r = 0.927; p= 0.003 • range sounds: - WH: 175-350 - WH harmonics 475-600 **Trachea:** F50 Baseline • Inspiration: responders 687 ± 128; non-responders (568 ± 209) • Expiration: responders 710 ± 110; non-responders 608 ± 59 F50 After BPT • Inspiration: responders 835 ± 120; non-responders 558 ± 216 • Expiration: responders 909 ± 81; non-responders 568 ± 133 F50 After SALB • Inspiration: responders 773 ± 113; non-responders 558 ± 186 • Expiration: responders 781 ± 57; non-responders 575 ± 112 • Range sounds of WH: up to 1200 • ΔF50e on responders: After BPT-Baseline: p<0.001 After bronchodilator-Baseline: p<0,01
Nukaga, 2018	Japan	Asthma: • n=64: 26 ♀ 38 ♂ • 8.9 ± 2.8 years	Treatment (bronchodilation): • 1 time • β2 agonist • procaterol 30 μg + saline 2.0 ml	• Microphone (handheld) over AS-R • Normal breathing • Standing position • Recordings for ≥10 s: - Baseline - After inhalation (15 min)	• Microphone • Pneumotachograph • Sound-amplifying unit for 100–2500 Hz sounds • Sound spectrometer (10,240 hz)	• Sampling frequency at 10,240 Hz • Band-pass filter at 40–2500 Hz band-pass filter • FFT • Spectrograph (Hanning window) • HFI and HFE determined manually	• F50 (Hz) • F99 (Hz) • spectrum curve indices: - Spectral slope (-dBm/octave) - A3/AT (%) - B4/AT (%) - P3/PT (%) - P4/PT (%) • RPF50 (dBm/Hz) • RPF75 (dBm/Hz)	Baseline vs after inhalation • F50: 180.8 ± 86.0 vs 188.1 ± 88.3 p=0.127 • F99: 907.3 ± 270.1 vs 953.3 ± 219.2 p=0.122 • Slope: 24.9 ± 9.7 vs 25.3 ± 10.5 p=0.735 • A3/AT: 12.1 ± 1.9 vs 13.7 ± 1.6 p<0.001 • B4/AT: 7.3 ± 1.4 vs 8.3 ± 1.3 p=0.001 • P3/PT: 12.4 ± 2.2 vs 13.0 ± 3.6 p=0.243 • P4/PT: 7.3 ± 1.5 vs 7.8 ± 2.9 p=0.263 • RPF50: 6.00 ± 1.5 vs 7.2 ± 1.5 p<0.001 • RPF75: 6.10 ± 1.6 vs 7.80 ± 2.0 p<0.001

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
Pasterkamp, 1997	Canada	Asthma: • n=15 (no gender specified) • 12 ± 2 years Healthy: • n=9 (no gender specified) • 12 ± 2 years	Direct BPT: • methacholine • starting concentration of 0,25 mg/ml • doubling concentrations for 2 min until drop of FEV1≥20% (Responders) Bronchodilatation: • salbutamol • 2 times • 200 μg	• Sensors over TR and chest (AS-R, AS-L, PI-R, PI-L, AI-R, AI-L, AM-R) • Nose clip • Flow at 2 l/s • Sitting position • Recording for at least 40 s: - Baseline - After BPT	• Piezoelectric accelerometers • Heated pneumotachograph • Pressure transducer • Analog-to-digital converter	• Sampling rate at 10,240 points/s High-pass filter (1st order Butterworth, cut-off 50 Hz) and amplified (200 x) • Low-pass filter (8th order Butterworth, cut-off 2.5 KHz) • Sound signals parsed in segments of 2048 data points with 50% overlap of points between successive segments. • Segments windowed with Hanning function • FFT • Frequency content between 100 and 2000 Hz. • Auditory confirmation to confirm wheeze detection	• Power (at low and high frequencies) (dB) • F50 (Hz) • F99 (Hz)	**Responders** Baseline • Power at low freq (100–200 Hz): Trachea: 53.3 (Insp); 55.6 (Exp) Chest: 47.2–52.4 (Insp); 39.0–45.0 (Exp) • Power at high freq (400–20000 Hz): Trachea: 44.6 (Insp); 49.5 (Exp) Chest: 17.1–27.9 (Insp); 4.9–18.0 (Exp) • F50: Trachea: 463 (Insp); 566 (Exp) Chest: 142–181 (Insp); 115–167 (Exp) • F99: Trachea: 1583 (Insp); 1354 (Exp) Chest: 403–555 (Insp); 397–616 (Exp) After BPT • Power at low freq (100–200 Hz): Trachea: 53.7 (Insp); 55.3 (Exp) Chest: 43.5–49.6 (Insp); 41.7–46.7 (Exp) • Power at high freq (400–20000 Hz): Trachea: 44.7 (Insp); 48.7 (Exp) Chest: 17.4–26.2 (Insp); 9.2–22.2 (Exp) • F50: Trachea: 504 (Insp); 589 (Exp) Chest: 146–202 (Insp); 126–183 (Exp) • F99: Trachea: 1498 (Insp); 1399 (Exp) Chest: 413–538 (Insp); 293–833 (Exp) **Non-Responders** (*continued on next page*)

Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
								Baseline • Power at low freq (100–200 Hz): Trachea: 52.2 (Insp); 53.2 (Exp) Chest: 48.7–53.4 (Insp); 39.7–46.6 (Exp) • Power at high freq (400–20000 Hz): Trachea: 46.1 (Insp); 52.7 (Exp) Chest: 19.9–27.8 (Insp); 6.3–20.7 (Exp) • F50: Trachea: 593 (Insp); 780 (Exp) Chest: 138–179 (Insp); 125–157 (Exp) • F99: Trachea: 1533–1634 (Insp1354-1477 (Exp) Chest: 403–678 (Insp); 293–833 (Exp) After BPT • Power at low freq (100–200 Hz): Trachea: 54.3 (Insp); 55.6 (Exp) Chest: 45.3–50.7 (Insp); 41.8–47.0 (Exp) • Power at high freq (400–20000 Hz): Trachea: 46.1 (Insp); 52.0 (Exp) Chest: 19.8–26.3 (Insp); 8.7–21.6 (Exp) • F50: Trachea: 529 (Insp); 725 (Exp) Chest: 151–193 (Insp); 127–168 (Exp) • F99: Trachea: 1533 (Insp): 1457 (Exp) Chest: 490–626 (Insp); 314–673 (Exp)

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
Sanchez, 2001	Canada	Asthma: • n=40: 20 ♀ 20 ♂ • 5.2 ± 1 year Healthy: • n=40: 22 ♀ 18 ♂ • 5.6 ± 1 year	Direct BPT: • methacholine • from 0,06–8 mg/m • until drop of PtcO2>20%	• Sensor over TR and AS-R • Flow between 0.4 and 0.6 l/s • Recording ≥1 min: - Baseline - After BPT	• Piezoelectric accelerometers (100–1200 Hz) • Pneumotachograph	• Sampling rate at 10 kHz • High-pass filter at 7.5 Hz (1st order Butterworth filter) and low-pass filter at 2.5 kHz (8th order Butterworth filter) • FFT (Hanning data window, 1024 data points, 75% overlap) • Frequency content between 100 and 2000 Hz	• F50 (Hz) • F99 (Hz) • Intensity of LFr (Plow= 100–200 Hz) and HFr (Phigh= 400–2000 Hz) bands. (dB)	**Asthmatic** Baseline • F50 = 501.32 ± 12.9 • F99 = 718.50 ± 12.94 • Plow = 0.000159±7e-6 • Phigh = 0.000163±7e-6 After BPT • F50 = 521.23 ± 18.1 • F99 = 798.68 ± 31.58 • Plow = 0.6509±7e-3 • Phigh = 0.6026±1e-2 Baseline < After BPT (for F50, F99, Plow and Phigh): p<0,05 **Healthy** Baseline • F50 = 498.28 ± 24.06 • F99 = 719.50 ± 23 • Plow = 0.000160±1e-5 • Phigh = 0.000164±8e-6 After BPT • F50 = 539.08 ± 29 • F99 = 845.13 ± 45.54 • Plow = 0.6579±9e-3 • Phigh = 0.6232±2e-2 Baseline < After BPT (for F50, F99, Plow and Phigh): p<0,05 After BPT: Healthy > Asthmatic (for F50, F99, PHigh): p<0,05
Sánchez, 2002	Canada	Acute bronchiolitis (AB): • n=76 28 ♀ 48 ♂ • 5.5 ± 0.7 months Random subgroup of 22 participants Recurrent wheezing (RW): • n=32: 12 ♀ 20 ♂ • 11.2 ± 2 months	Treatment (bronchodilation): • salbutamol • usual dosage	• Sensors over AI-R, AI-L • Flow between 0.1 ± 0.02 l/s • Lying position (spontaneous sleep) • Recordings for 40 s: - Baseline - After bronchodilatation (20 min)	• Piezoelectric accelerometers (100–1200 Hz) • Pneumotachograph	• Sampling rate at 10 kHz • High-pass filtered at 7.5 Hz (1st order Butterworth filter) and low-pass at 2.5 kHz (8th order Butterworth filter). • Signal processing with FFT (Hanning data window, 1024 data points, 75% overlap) • Frequency content between 100 and 1000 Hz	• Presence of: WH, CR + WH • Duration of WH or CR + WH (ms) • Minimum frequency (Hz) • F50 (Hz) • F99 (Hz) • WH% • Sound spectra range (Hz)	**AB group** • 53% with WH + 47% with CR + WH • Minimum frequency: 252 ± 10 (WH) vs 162 ± 16 (CR + WH) p<0.001 • WH% vs range displacement including F50 & F99: r=0.81 p<0.001 • Sound spectra between 100 and 600Hz **Subgroup of 22 subjects** • 50% with WH + 50% with CR + WH • Duration: 250 ± 22 (WH) vs 35 ± 11 (WH + CR) p <0.001 • WH with classical harmonics and sinusoidal wave vs WH + CR with none p<0.001 • Minimum frequency on WH: 252 ± 10 vs WH + CR: 162 ± 16 p <0.001

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
								• Different response to salbutamol between WH participants (9/11) vs WH + CR participants (3/11). p<0.001 **RW group** • 94% with WH + 6% with CR + WH • WH% vs range displacement including F50 & F99: r=0.88. p<0.001 • Sound spectra between 100 and 900 Hz **After Bronchodilatation** • No. of obstructive episodes in AB participants with WH (26/40) vs with WH + CR (8/36) p<0.01 • No. of obstructive episodes in AB vs RW participants (30/34) p<0.01
Tabata, 2018	Japan	Asthma: • n=49: 33 ♀ 16 ♂ • 10.2 ± 2.5 years	Direct BPT: • methacholine • diluted two-fold with saline • series of 10 strengths, from 25 mg/mL to approximately 49 μg/mL • until Rrs doubled the baseline value. • 1 time Bronchodilatation: • β2 agonist	• Microphone (handheld) over AS-R • Normal breathing • Standing position • Recordings for ≥10 s: - Baseline - After BPT (immediately) - After Bronchodilatation (15 min)	• Microphone • Pneumotachograph • Sound spectrometer (10,240 hz)	• Sampling frequency at 10,240 Hz • Band-pass filter at 40–2500 Hz band-pass filter • FFT • Spectrograph (Hanning window) • HFI and HFE determined manually	• F50 (Hz) • F99 (Hz) • spectrum curve indices: - Spectral slope (-dBm/octave) - PT (%) - AT - A3/AT (%) - B4/AT (%) - P3/PT (%) - P4/PT (%) • RPF50 (dBm/Hz) • RPF75 (dBm/Hz)	Baseline vs after BPT vs after bronchodilatation: • F50: 145.6 ± 30.9 vs 144.1 ± 27.5 vs 139.6 ± 32.80 • F90: 722.3 ± 207.0 vs 789.9 ± 294.3 vs 754.0 ± 263.9 • Slope: 23.7 ± 8.9 vs 20.0 ± 10.9 vs 24.8 ± 11.0 • PT: 146.9 ± 58.3 vs 170.4 ± 87.5 vs 146.3 ± 76.0 • AT: 5584.7 ± 1341.3 vs 6377.1 ± 2113.2 vs 5741.6 ± 1785.4 • A3/AT: 12.5 ± 2.2 vs 10.0 ± 2.1 vs 12.5 ± 2.7 • B4/AT: 7.6 ± 1.6 vs 5.5 ± 1.6 vs 7.4 ± 1.8 • P3/PT: 56.8 ± 15.7 vs 53.9 ± 13.5 vs 59.3 ± 16.0 • P4/PT: 44.7 ± 14.2 vs 42.4 ± 12.3 vs 46.9 ± 14.5 • RPF50: 5.8 ± 1.1 vs 4.3 ± 1.3 vs 6.06 ± 1.4 • RPF75: 6.7 ± 1.7 vs 4.0 ± 1.4 vs 6.6 ± 2.2 Significant differences: Baseline vs after BPT: AT (p=0,001); A3/AT (p<0,001); B4/AT (p<0,001); RPF50 (p<0,001); RPF75 (p<0,001) After BPT vs after bronchodilation: P3/PT (p=0,007); P4/PT (p=0,011);

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Table 2 (*continued*)

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
								AT (p=0,015); Slope (p=0,012); A3/AT (p<0,001); B4/AT (p<0,001); RPF50 (p<0,001); RPF75 (p<0,001) Baseline vs after bronchodilation: none
Tal, 1991	United States of America	Bronchiolitis: • n=16: 4 ♀ 12 ♂ • 9.4 [1–23] months	Treatment (bronchodilation): • salbutamol: • 0.03 ml of nebulized solution per kilogram of body weight • the 0,5% nebulizer solution contains 0,9% saline that is added to a total volume of 2 ml.	• Sensors over AS-R or PS-R or PS-L (depending on participants comfort position) • Awake, resting on a parent's lap or bed •Recordings for 10–15 s: - Baseline - After salbutamol (10–15 min)	• Microphone • Respiratory inductive plethysmography • Four-channel frequency modulation instrumentation • Analog-to-digital converter • Loudspeakers or headphones	• Sampling rate at 5120 Hz per channel • Low-pass filtered with 6th-order Butterworth filter at 1200 Hz • FFT to 1024 data points at 100 ms segments with 50% overlap into adjacent 100 ms segments and Hanning window •Segments of 100 ms were marked as wheezing or normal based on (1) distinct peaks in the frequency domain. (2) periodic waveform appearance in the time domain. (3) auditory verification on playback.	• wheezes waveforms (sinusoidal or complex repetitive) • WH% • I/E ratio • RR (breaths/min) • avgFw (Hz) • Responders: WH %<2% or drop of WH% > 10%	Before salbutamol administration: • Wheezes waveforms: 14 complex repetitive 1 sinusoidal Before vs after salbutamol administration: •7 responders: WH%: 47 ± 26 vs 20 ± 25 I/E ratio: 0.7 ± 0.2 RR: 65 ± 8 vs 57 ± 7; p<0.05 avgFw: 230 ± 5 vs 255 ± 101 •9 non-responders: WH%: 31 ± 13 vs 38 ± 12 I/E ratio: 0.7 ± 0.1 RR: 53 ± 10 vs 56 ± 9 avgFw: 271 ± 64 vs 206 ± 21; p<0.05

Legend: Data are presented as mean ± standard deviation or median [interquartile range], unless otherwise stated; ♀-female; ♂-male; A1000-area under the curve>1000Hz (dBm/Hz); A3-third area under the curve; AI - anterior inferior; AM-anterior middle; ARS-adventitious respiratory sounds; AS - anterior superior; AT-total area under the curve of 100 Hz to the highest frequency of the of the of the dBm power spectrum; avgFw-average peak frequency; AX-axilla; B4-forth area under the curve; BPT-bronchial provocation test; CG-control group; CORSA-computerized respiratory sounds analysis; CR-crackle; EV – energy values as an arbitrary value which correlates with loudness; F25, F50, F75, F90, F95, F99 - frequencies of 25, 50, 75, 90, 95, 99% respectively of the spectral sound measured (Hz); FD-fractal dimension; FEV1-forced expiratory volume on the 1st second; FFT-Fast Fourier transformation; Fmax-maximal frequency; Fmin-minimal frequency; GINA-global initiative for asthma; HF-high flow; HFr-high frequency; HFE-highest frequency on breath expiratory sounds; HFI-highest frequency on breath inspiratory sounds; I-inferior; I/E – inspiratory/expiratory; IC-Integrated Circuit AKA Digital voice; IG-intervention group; L-left; LFr - low frequency; LF – low flow; P-power; P3-third area of power area; P4-forth area of power area; PEF-peak expiratory flow; PI-posterior inferior; PR-power ratio; PS-posterior superior; PtcO2- transcutaneous oxygen tension; PT-total power area; R/L-right to left; RMS-root mean square of the sound signal; RPF50 or 75-ratio power/frequency at 50 or 75% of the highest frequency of the dBm power (dBm/Hz); R-right; RR-respiratory rate; Te-expiratory time; Ti-inspiratory time; TR-trachea; WH %-wheeze occupation rate; WH-wheeze.

Table 3
Computerized respiratory sounds in paediatrics: controlled intervention studies (n=1).

Author, Year	Country	Participants	Intervention	Data collection procedures	Recording Device	Data analysis	Outcome measures	Findings
Beck, 2007	Israel	Bronchiolitis: Total: • n=27: 8 ♀ 19 ♂ • 4.4 ± 0.8 months Group Epinephrine: • n=12: 4 ♀ 8 ♂ • 4.9 ± 0.8 months Group Salbutamol: • n=15: 4 ♀ 11 ♂ • 4 ± 1.35 months	Treatment with a single dose of: 1 mgr nebulized epinephrine or 2.5 mgr nebulized salbutamol.	• Sensors over AX-R, AX-L, AI-R, AI-L • Breathing without crying • Recording for 5 min • Ambient noise – with an air-coupled microphone placed near the participant Breathing activity - with chest impedance	• Piezoelectric contact sensors (linear ±3 dB frequency response from 75 to 2000 Hz, a resonance at 2.7 kHz, a useable range that extends beyond 4 kHz) • Microphone • PulmoTrack system Phono pneumograph	• Pneumotrack: amplification x3000; band-pass filtration 80–4000 Hz at 28 dB/OCT • WH detection: FFT CR counter algorithm (confirmed manually by 2 pneumologists)	• WH %-Ttot • No. CR/ breath cycle	•WH%-Ttot: After Epinephrine Salbutamol p 0 s 9.1 ± 3.4 5.5 ± 3.08 0.53 10 s 5.47 ± 3.26 9.11 ± 2.52 0.15 30 s 7.1 ± 3.63 11.9 ± 4.5 0.20 •CR/breathing cycle: After Epinephrine Salbutamol p 0 s 1.88 ± 0.59 1.74 ± 0.42 0.68 10 s 2.48 ± 0.92 1.14 ± 0.23 0.37 30 s 2.26 ± 0.7 . 1.31 ± 0.33 0.35

consistent increase with treatments in asthmatics [59,61,68,74].

F50 ranged between 194 ± 26 [52] and 521 ± 18 Hz [62] in healthy participants and between 180 ± 86 [60] and 909 ± 81Hz [56] in asthmatic participants (Fig. 2).

Bronchial provocation tests increased F50 in healthy participants (up to 40%) and those with asthma with methacholine (up to 12%) [62] and with histamine (up to 28%) [56]. When β2-agonist was used in asthmatic participants no significant changes were found [21,60,61,68], but one [47] of the two [47,63] studies with bronchiolitis showed a significant increase of F50.

Sound intensities of 14.3 ± 1.7 dB/oct and between −1.7 and 66.5dB/oct were detected in spectral slopes of 300–700Hz and 600–1200Hz, respectively, in healthy participants [44,46]. In asthmatic children and children with LRTI sound intensities between 14.8 and 31.5 dB/oct [58] and −1.7 and 66.5dB/oct [46] were detected in a spectral slope of 600–1200Hz, respectively. Asthmatic participants with β2-agonist treatments showed a consistent increase from 0.16 to 2.18% on power in a spectral slope of 600–1200Hz [58,60,72].

3.8. Adventitious respiratory sounds

ARS characteristics were evaluated in healthy participants [29,45,66] and in participants with bronchiolitis [47,48,63,64], asthma [29,45,51,53], atelectasis [40], recurrent wheezing [63], acute respiratory infection [66] and non-specified health status [41,53]. A total of 13 studies analysed wheezes [29,40,41,45,47,48,51,53,56,57,63,64,66] and the outcomes measures used were: wheeze occupation rate [29,48,57,63,64], presence of wheezes [40,45,48,63,66], duration [41,47,51,53,63] and highest [51,56,57,66,75] and lowest frequency [47,56,63]. Breathing phases (inspiration and expiration) were considered in two studies [29,53] and only one analysed both normal and forced breathing [51]. Pre-post bronchial provocation test was assessed in one study [45] and pre-post treatment in three studies [40,48,57].

The presence of wheeze was detected in 11–33% of participants with bronchiolitis [48,63], 9% of participants with acute respiratory infection [66], 0%–18.3% of healthy and asthmatic participants [45], 94% of wheezing participants (53% in the absence of crackles and 47% in association with crackles [63]) and in participants with atelectasis, but quantification was not reported [40].

Wheeze occupation rate was 0% [29] in healthy participants, varied in bronchiolitis from 47 ± 26% before treatment [57] to 2 ± 2.7% after hypertonic saline nebulization [48] over the trachea and during inspiration in asthmatic children from 0% to 24.7 ± 25.9% [29]. For participants with non-specified health status, these values were between 1.6 ± 1.4% over the trachea and 6.1 ± 4.6% over the mouth [41].

Overall, the duration of wheezes ranged from 24 ms [47,63] in bronchiolitis to 400 ms [53] during the inspiration in asthma. Different durations were observed, ranging from 24 to 277 ms in bronchiolitis [47,63], from 40 [53] to 350 ms [51] in asthmatics and from 32 to 400 ms in other several respiratory conditions (e.g., cystic fibrosis, LRTI or pre-school wheezes) [53]. In participants with non-specified health status, duration ranged between 42 and 190 ms [41].

Frequency values of wheezes were between 146 and 335 Hz in bronchiolitis [57,63] and between 175 and 1200 Hz over the trachea in asthmatic participants [29,51,56]. For participants with non-specified health status, the values were between 293 and 1033Hz [41].

Only four studies analysed crackles [40,53,63,64], but none used the same outcome measure. Crackles were present in 6% of participants with recurrent wheezing [63].

Respiratory physiotherapy reduced the number of crackles in participants with atelectasis [40] by 20.8%. Duration of crackles was reported in only one study and ranged between 6 and 20 ms in participants with asthma, cystic fibrosis, LRTI and pre-school wheezes [53]. Only one study counted crackles per breath cycle after treatment (epinephrine and salbutamol) in bronchiolitis and 1.14 ± 0.23 to 2.48 ± 0.97 crackles were reported [64].

4. Discussion

The major findings emerging from this systematic review were: i) high heterogeneity in the procedures, outcomes and outcome measures used to record and analyse respiratory sounds in paediatrics; ii) F50 is the most used outcome measure for NRS and presence of wheezes and their occupation rate (WH%) for ARS; iii) asthmatic participants showed highest values on F50 than other populations, F50 tend to increase with provocation test (histamine and methacholine) and decrease with treatments (B2-agonist); iv) breath sounds intensity decrease with bronchoconstriction; v) crackles were related to the presence of atelectasis.

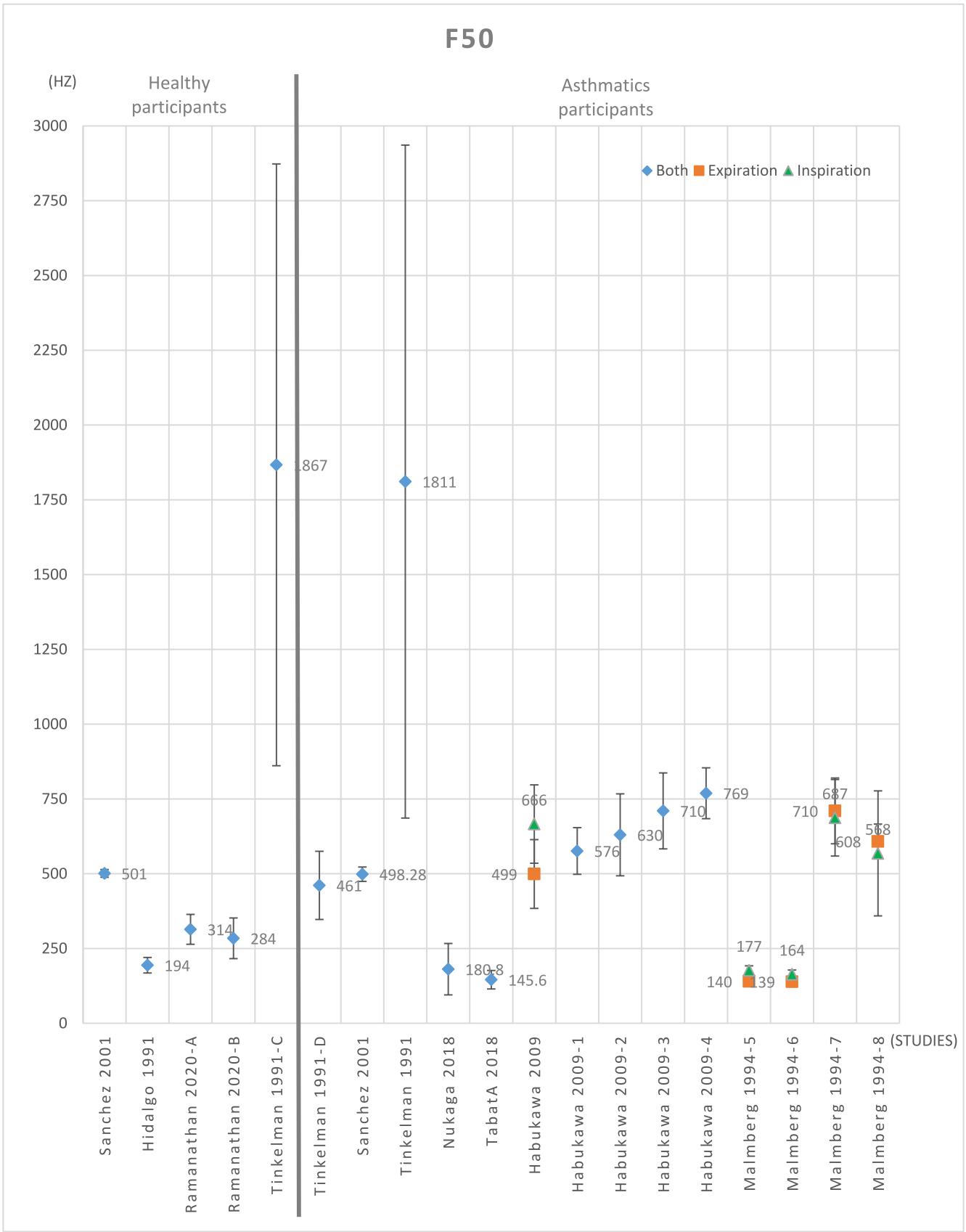

Fig. 2. Mean and standard deviation (whenever reported) of the median frequency of the spectral sound (F50) in a) Healthy participants and in b) asthmatic participants, Legend: A – 1 min after birth; B – 2 h after birth; C - with wheezes; D - without wheezes; 1 – GINA severity grade 1; 2 - GINA severity grade 2; 3 - GINA severity grade 3; 4 - GINA severity grade 4; 5 – responders, at chest; 6 – non-responders, at chest; 7 – responders, at trachea; 8 – non-responders, at the trachea.

4.1. Respiratory sound acquisition

The CORSA guidelines recommended reporting the flow rate and type of breathing [76] since they influence respiratory sounds amplitude and frequency [21,77–79], however, these parameters were not reported in 21.5% of the included studies [29,45,48,53,54,57,80]. The absence of reporting these parameters has been previously acknowledged [81] and is strongly recommended to facilitate comparisons across studies.

Microphones were the equipment most used to acquire respiratory sounds in children. Despite the need of reporting the specificities of the microphone used, this device seems to be the best option due to its high practicability, capacity for continuous monitoring [17] and accuracy when compared with stethoscopes [17,78]. Nevertheless, digital stethoscopes are more available than microphones on a daily basis [53,82,83], and may therefore be the first choice for studies conducted in clinical settings with large samples.

The literature suggests the trachea and left and right posterior inferior chest as minimum essential recording locations for lung auscultation [84]. Other recommended locations are left and right anterior superior chest and optionally right and left axillary chest [84]. Nevertheless, only 30% of the included studies used the trachea and 12–23% used the right/left posterior inferior chest. Moreover, 46% of the studies used one single location.

Characteristics of respiratory sounds are affected by the dimension of the airways but other factors such as airflow, sex and chest location influence their production [69,81,85–87]. A variety of locations as well as a single location [84] for acquiring the sound will hinder comparisons across studies. A compliance to sound acquisition guidelines is strongly recommended in future studies to allow interpretation and generalization of respiratory sound findings.

4.2. Respiratory sound analysis

The sound bandwidth of the studies ranged from 40 Hz to 2.7 KHz. These values include the recommended minimum limit of 60–100 Hz and a maximum over 2 KHz for wheeze detection but may miss the detection of other ARS, such as crackles, which can go up to 6 KHz [88,89].

4.3. Normal respiratory sounds

Spectral slopes from 600 to 1200Hz were higher in healthy [44,46] than asthmatic participants [58] and in these, the values consistently increased after treatment [58,60,72]. Similar results have been found previously in studies comparing either healthy vs. asthmatics or asthmatic before vs. after bronchial provocation tests [90–93], corroborating the utility of this outcome measure as a bronchoconstriction evaluation.

Another commonly reported outcome measure was the frequency of normal respiratory sounds, F50, which, similarly to other studies [21,94,95], showed an increase in asthmatic participants after bronchial provocation tests [56]. Nevertheless, this significant increase was not observed in all studies [67,72], maybe due to the fact that the frequency content can reach higher values during a late asthmatic response than on an early asthmatic response. It seems, therefore, that an increase of pitch and decrease in the intensity of lung sounds is a finding of airway narrowing [90,91,94]. In sum, breath sound intensity decreases and F50 increases when maximal bronchial constriction occurs.

4.4. Adventitious respiratory sounds

Wheezes were the adventitious respiratory sound most reported. In a previous review, mostly with adults, the wheeze occupation rate seemed to be the most promising parameter to be used as an outcome measure, with high/medium effect sizes (0.62–1.82), when compared with other wheezing (timing, presence, number, frequency) and crackles variables [96].

Overall, the duration of wheezes ranged from 24 ms [47,63] in bronchiolitis to 400 ms [53] during inspiration in asthma. The American Thoracic Society has set a minimum duration of 250 ms for a wheeze [15,97], however, lower minimum values between 80 and 100 ms are currently reported [21,98]. In this review, shorter lengths of wheezes were found, i.e., between 24 ms in children up to 2 years [47,63] and 32 ms in children and teenagers [53]. Since the respiratory rate is higher in younger individuals [99–101], it is likely that the duration of these sounds within the inspiratory or expiratory phases are also shorter than in older individuals. This difference highlights the need for adventitious respiratory sounds reference values in paediatrics and may eventually be not as useful as the wheeze occupation rate since their absolute length values are age-dependent on this population.

Paediatrics are more likely to develop atelectasis than adults [102] and the computerized analysis identified crackles that decreased after physiotherapy using inspiratory manoeuvres in children with atelectasis [40]. This finding corroborated that crackles presence might be related to atelectasis [21,103–105].

5. Conclusion

Respiratory sounds show different acoustic properties in healthy children and children with different respiratory disorders and thus may be a useful parameter to be used in the diagnosis and monitoring of children. However, respiratory sound acquisition procedures and analysis varied widely across studies which limited the pooling of the results and establishment of sound patterns in children. Nevertheless, this systematic review provides information on the most and less used protocols and outcome measures for respiratory sounds acquisition and analysis in children. Breath sound intensity, spectral slope, the presence of crackles the presence and occupation rate of wheezing are common and valuable outcome measures to examine the respiratory system.

Regarding Wheezes the cut-off values for sound frequency should be, for this population, in a range between less than 60 Hz–2000 Hz. For wheezes the minimal lengths can be as low as 24 ms. Without reference values indexed for different respiratory frequencies this outcome measure is not very informative and their presence or occupation rate is way more relevant. Gradient slopes that show intensity increase as well as breath sounds that show intensity decrease are a useful outcome measure to evaluate bronchial constriction. Crackles are useful to evaluate atelectasis and crackles can be found on values as high as 6000 Hz.

Future studies should focus on understanding the reason for studies not to comply with CORSA recommendations and eventually update those guidelines, namely including paediatric specificity regarding positioning, devices, locations and ventilation's flow and type. Cutoff values must be adapted to ensure adventitious sounds findings and reference values related to ventilation's changes due to age are important.

Declaration of interest

The authors report no conflicts of interest.

CRediT authorship contribution statement

Verónica Abreu: Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Ana Oliveira:** Conceptualization, Writing – review & editing, Visualization. **José Alberto Duarte:** Conceptualization, Writing – review & editing, Visualization, Supervision. **Alda Marques:** Conceptualization, Writing – review & editing, Visualization, Supervision.

Appendix A. PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	cover
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	√
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3–4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	CD
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7–21
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7–21
Synthesis of results	21	Present the main results of the review. If meta-analysis done, include for each, including confidence intervals and measures of consistency.	5–25
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	25
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25–27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

Legend: CD=cannot determine; NA, not applicable.

Appendix B. Study quality assessment tables

Quality Assessment for Observational Cohort and Cross-Sectional Studies:

	Adachi, 2016	Beck, 2007	Bokov, 2016	Ellington et al., 2014	Faber, 2015	Gnitecki, 2004	Hidalgo, 1991	Kevat, 2017	Mazic, 2003	Murayama, 2019	Pasterkaamp, 1996	Rietveld, 1999	Sánchez, 2005	Shioya, 2018	Tinkelman, 1991	Ramanathan, 2020
reviewer	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b	1 2 b
1	Y Y	Y Y	Y Y	Y Y	Y Y	Y Y	Y Y	Y Y	Y Y	N Y	Y Y	Y Y	Y Y	Y Y	Y Y	Y Y
2	Y Y	Y Y	Y Y	Y Y	Y Y	N N	O Y	N N	Y Y	Y Y	Y Y	Y Y	Y Y	Y Y	N N	Y Y

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(*continued*)

	Adachi, 2016			Beck, 2007			Bokov, 2016			Ellington et al., 2014			Faber, 2015			Gnitecki, 2004			Hidalgo, 1991			Kevat, 2017			Mazic, 2003			Murayama, 2019			Pasterkaamp, 1996			Rietveld, 1999			Sánchez, 2005			Shioya, 2018			Tinkelman, 1991			Ramanathan, 2020		
reviewer	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b
3	O	N		Y	N		Y	Y		O	O		Y	Y		CD	CD		O	N		O	O		O	N		O	O		O	N		O	O		O	O		Y	O		O	O		Y	Y	
4	O	Y		Y	Y		Y	Y		Y	Y		NR	N		NR	Y		O	O		N	Y		Y	O		Y	Y		N	N		N	N		O	Y		Y	Y		O	O		Y	Y	
5	N	NA		O	NA		N	N		N	Y		N	Y		N	N		N	O		O	N		O	N		N	N		N	N		N	N		N	N		N	N		N	N		N	Y	
6	Y	N		Y	N		Y	y		O	N		Y	O		Y	N		O	Y		O	Y		Y	Y		Y	Y		O	O		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y	
7	Y	NA		Y	NA		O	O		O	O		Y	Y		CD	O		O	N		O	O		O	O		O	O		O	O		Y	O		Y	Y		CD	O		O	O		Y	Y	
8	O	Y		N	Y		N	O		O	O		N	Y		Y	O		O	O		N	Y		N	Y		Y	Y		O	Y		Y	Y		N	N		N	N		N	Y		O	O	
9	N	Y		N	Y		N	O		N	O		Y	Y		CD	N		N	O		N	O		N	Y		Y	Y		Y	Y		Y	Y		N	Y		N	N		O	Y		Y	Y	
10	Y	Y		Y	Y		N	O		N	O		N	N		Y	Y		N	O		N	O		N	N		N	N		N	N		Y	N		Y	Y		N	O		N	N		Y	Y	
11	N	Y		Y	Y		Y	Y		N	Y		Y	Y		N	N		N	Y		N	Y		N	N		N	N		N	Y		N	Y		Y	Y		Y	O		Y	O		Y	Y	
12	O	Y		O	N		O	O		O	O		NR	O		NR	NR		O	O		O	O		O	O		O	O		O	N		O	Y		O	N		CD	Y		O	O		Y	Y	
13	Y	N		Y	N		Y	O		Y	O		Y	Y		NR	Y		Y	O		Y	Y		Y	O		O	O		Y	O		N	Y		Y	Y		Y	Y		N	O		Y	Y	
14	N	NA		N	NA		N	N		N	O		N	O		CD	O		N	O		N	Y		N	O		O	O		N	O		N	Y		N	O		CD	Y		N	N		CD	Y	
Quality Rating	**F**	**F**		**F**	**G**	**G**	**G**	**F**	**F**	**F**	**F**	**F**	**G**		**G**	**G**	**P**		**P**	**P**	**P**	**P**	**F**	**P**	**P**	**P**	**P**	**P**	**F**	**F**	**F**	**F**	**F**	**F**	**G**	**G**	**G**	**G**	**G**	**G**	**G**		**G**	**G**	**P**	**P**	**P**		**G**	**G**	**G**

Legend: b=both; Y=Yes, N=No; O=Other (CD=cannot determine; NA, not applicable; NR, not reported), F=Fair; G=Good, P=Poor. Questions: 1. Was the research question or objective in this paper clearly stated?, 2. Was the study population clearly specified and defined?, 3. Was the participation rate of eligible persons at least 50%?, 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?, 5. Was a sample size justification, power description, or variance and effect estimates provided?, 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?, 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?, 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?, 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?, 10. Was the exposure(s) assessed more than once over time?, 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?, 12. Were the outcome assessors blinded to the exposure status of participants?, 13. Was loss to follow-up after baseline 20% or less?, 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?.

Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group.

	Enseki, 2019			Fenton, 1985			Habukawa 2009			Habukawa, 2010			Kondo, 2018			Malmberg, 1994			Nukaga, 2018			Pasterkamp, 1997			Sanchez, 2001			Sánchez, 2002			Tabata, 2018			Tal, 1991		
reviewer	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b	1	2	b
1	Y	Y		Y	Y		Y	N		Y	Y		y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y	
2	N	N		N	N		N	Y		N	N		y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y	
3	N	N		N	N		O	P		CD	O		CD	Y		Y	N		CD	O		N	N		NR	O		NR	NR		CD	O		Y	O	
4	CK	O		NR	O		Y	N		Y	O		CD	O		O	Y		CD	O		NR	O		NR	Y		NR	Y		CD	O		Y	Y	
5	N	N		N	O		O	Y		CD	Y		CD	Y		O	O		CD	Y		NR	O		NR	Y		NR	Y		CD	Y		O	N	
6	Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		N	Y		Y	Y		Y	Y	
7	Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y	
8	NR	O		NR	O		O	O		CD	O		CD	O		O	O		CD	O		NR	O		NR	O		NR	O		CD	O		O	O	
9	Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		N	Y		Y	Y		Y	Y		Y	Y		N	Y		Y	Y		N	Y	
10	Y	Y		N	N		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	Y		Y	O		Y	Y		Y	Y	
11	N	N		N	N		N	N		N	N		N	N		N	N		N	N		N	N		N	N		N	Y		N	N		N	N	
12	N	O		N	O		N	Y		N	N		N	N		N	N		N	N		N	N		N	N		N	Y		N	N		N	Y	
Quality Rating	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**G**	**F**	**F**	**F**	**F**	**F**	**G**	**F**	**F**	**F**	**F**	**F**	**G**	**G**	**F**	**F**	**F**	**F**	**G**	**F**	**F**	**F**	**F**

Legend: b=both; Y=Yes, N=No; O=Other (CD=cannot determine; NA, not applicable; NR, not reported), F=Fair; G=Good, P=Poor. Questions: 1. Was the study question or objective clearly stated?; 2. Were eligibility/selection criteria for the study population prespecified and clearly described?; 3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?; 4. Were all eligible participants that met the prespecified entry criteria enrolled?; 5. Was the sample size sufficiently large to provide confidence in the findings?; 6. Was the test/service/intervention clearly described and delivered consistently across the study population?; 7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?; 8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?;9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?; 10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?; 11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?; 12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?;

	Beck, 2007		
reviewer	1	2	both
1	Y	Y	
2	CD	N	
3	Y	Y	
4	Y	Y	
5	Y	Y	
6	N	Y	
7	Y	Y	

(*continued on next page*)

(*continued*)

	Beck, 2007		
reviewer	1	2	both
8	Y	Y	
9	N	NA	
10	N	CD	
11	Y	Y	
12	N	N	
13	NA	Y	
14	N	Y	
Quality Rating	**G**	**G**	**G**

Quality Assessment Tool for Randomized Controlled-Trial.

Legend: b=both; Y=Yes, N=No; O=Other (CD=cannot determine; NA, not applicable; NR, not reported), F=Fair; G=Good, P=Poor. Questions: 1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?; 2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?; 3. Was the treatment allocation concealed (so that assignments could not be predicted)?; 4. Were study participants and providers blinded to treatment group assignment?; 5. Were the people assessing the outcomes blinded to the participants' group assignments?; 6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?; 7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?; 8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?; 9. Was there high adherence to the intervention protocols for each treatment group?; 10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?; 11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?; 12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?; 13. Were outcomes reported or subgroups analysed prespecified (i.e., identified before analyses were conducted)?; 14. Were all randomized participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

Appendix C. Supplementary Tables

Table A
Synthesis of normal respiratory sound measurements (n=15).

Health Status	Autor, Year	Location		F50 (Hz)	F99 (Hz)	P low Freq (dB) at 100–200 Hz	P high Freq (dB) at 200–400Hz)	Spectral slope on 600–1200 Hz (dB/oct)	RPF50	RPF75	A3/AT
Healthy	Sanchez, 2001	AS-R + TR	Baseline	501,32 ± 12,9	718,50 ± 12,94	$0{,}000159 \pm 7^{-6}$	$0{,}000163 \pm 7^{-6}$ (at 400–2000 Hz)				
			After BPT	521,23 ± 18,1	798,68 ± 31,58	$0{,}6509 \pm 7^{-3}$	$0{,}6026 \pm 1^{-2}$ (at 400–2000 Hz)				
	Hidalgo, 1991	AS-R	inspiration (Median)	194 ± 26 195							
	Pasterkamp, 1996	Infants (1 ± 0,5 days) at low flow breathing	inspiration + expiration					17.7 ± 3.9 (300–700 Hz)			
		Children (7 ± 0,8 years) at low flow breathing	inspiration + expiration					17.2 ± 1.7 (300–700 Hz)			
		at high flow breathing	inspiration + expiration					14.3 ± 1.7 (300–700 Hz)			
	Ramanathan, 2020	Anterior and posterior right lung	1 min after vaginal delivery caesarean section combined	314 ± 50		0,27 ± 0,11	0,48 [0,39–0,56]				
			2 h after vaginal delivery caesarean section combined	284 ± 68		0,37 ± 0,15	0,38 [0,29–0,48]				
	Tinkelmann, 1991	PI-R	all	461 ± 114							
			2 years old	476 ± 88							
			3 years old	459 ± 119							
			4 years old	451 ± 120							
			5 years old	468 ± 140							
			6 years old	450 ± 93							
			with wheezing								

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Table A (*continued*)

Health Status	Autor, Year	Location		F50 (Hz)	F99 (Hz)	P low Freq (dB) at 100–200 Hz	P high Freq (dB) at 200–400Hz)	Spectral slope on 600–1200 Hz (dB/oct)	RPF50	RPF75	A3/AT
				1867 ± 1006							
	Shioya, 2018	AS-R	wheezing (median [range])		690 [260, 1260]			26.3 [3.1, 57.9]	6.7 [2.1, 14.3]	6.9 [1.8, 17.0]	12.7 [5.4, 19.9]
			no wheezing		675 [280, 1460]			27.7 [-1.7, 66.5	6.3 [2.3, 18.8	6.6 [2.5, 18.1	12.4 [7.0, 20.1]
			RSV		900 [400, 1340]			27.0 [14.5, 54.5]	7.1 [3.0, 11.2]	6.6 [1.8, 18.0]	12.4 [7.2, 20.1]
			no RSV		670 [260, 1460]			27.1 [-1.7, 66.5]	7.1 [3.0, 11.2]	6.6 [1.8, 18.0]	12.5 [5.4, 19.9
			hospitalization		815 [370, 1260]			27.0 [19.6, 33.8]	6.8 [5.1, 7.7]	5.8 [5.6, 7.4]	11.1 [7.2, 12.0]
			no hospitalization		680 [260, 1460]			27.1 [-1.7, 66.5	6.4 [2.1, 18.7]	6.7 [1.8, 18.0]	12.6 [5.4, 20.1]
			allergy		720 [380, 970]			31.5 [20.9, 64.9]	7.7 [4.1, 12.9]	8.0 [4.3, 14.1]	12.1 [9.9, 16.7]
			no allergy		680 [260, 1460			26.7 [-1.7, 66.5]	6.3 [2.1, 18.8	6.5 [1.8, 18.0]	12.5 [5.4, 20.1]
			atopic dermatitis		730 [350, 1130]			30.8 [3.9, 66.5]	7.6 [3.2, 16.5]	8.0 [3.4, 18.0]	12.3 [8.0, 17.0]
			no atopic dermatitis		670 [260, 1460]			26.7 [-1.7, 66.4]	6.2 [2.1, 18.7]	6.5 [1.8, 17.4]	12.6 [5.4, 20.1]
			family history		700 [280, 1340]			27.0 [-1.7, 66.5]	6.4 [2.1, 16.2]	6.9 [2.5, 18.0]	12.7 [7.0, 20.1]
			no family history		640 [260, 1460]			27.2 [-1.7, 66.4]	6.4 [2.3, 18.7]	6.3 [1.8, 16.8	11.9 [5.4, 19.0]
Asthma	Sanchez, 2001	AS-R + TR	Baseline	498,28 ± 24,06	719,50 ± 23,0	$0{,}000160 \pm 1^{-5}$	$0{,}000164 \pm 8^{-6}$				
			After BPT	539,08 ± 29,0	845,13 ± 45,54	$0{,}6579 \pm 9^{-3}$	$0{,}6232 \pm 2^{-2}$				
	Habukawa, 2009	AS-R	Expiration	499 ± 115							
			Inspiration	666 ± 131							
			Insp on grade 1 GINA	576 ± 78							
			Insp on grade 2 GINA	630 ± 137							
			Insp on grade 3 GINA	710 ± 127							
			Insp on grade 4 GINA	769 ± 85							
	Malmberg, 1994	AI-R (responders vs non responders)	PRÉ-BPT - inspiration	177 ± 15 vs 164 ± 14							
			PRÉ-BPT - expiration	140 ± 8 vs 139 ± 16							
			POST-BPT - inspiration	194 ± 17 vs 163 ± 12							
			POST-BPT - expiration	162 ± 12 vs 136 ± 9							
			POST-SALB - inspiration	181 ± 18 vs 169 ± 27							
			POST-SALB - expiration	136 ± 8 vs 128 ± 6							
		TR (responders vs non responders)	PRÉ-BPT - inspiration	687 ± 128 vs 568 ± 209							
			PRÉ-BPT - expiration								

(*continued on next page*)

Table A (*continued*)

Health Status	Autor, Year	Location		F50 (Hz)	F99 (Hz)	P low Freq (dB) at 100–200 Hz	P high Freq (dB) at 200–400Hz)	Spectral slope on 600–1200 Hz (dB/oct)	RPF50	RPF75	A3/AT
				710 ± 110 vs 608 ± 59							
			POST-BPT - inspiration	835 ± 120 vs 558 ± 216							
			POST-BPT - expiration	909 ± 81 vs 568 ± 133							
			POST-SALB - inspiration	773 ± 113 vs 558 ± 186							
			POST-SALB - expiration	781 ± 57 vs 575 ± 112							
	Tinkelman 1991		wheezing	1811 ± 1125							
	Kondo, 2018	AS-R	baseline		931.6 ± 268.0				6.00 ± 1.7	5.80 ± 1.3	12.1 ± 1.7
			after treatment		970.1 ± 201.3				7.47 ± 1.8	7.00 ± 1.4	13.6 ± 1.5
	Nukaga, 2018	AS-R	baseline	180.8 ± 86	907.3 ± 270.1			24.9 ± 9.7	6.00 ± 1.5	6.10 ± 1.6	12.1 ± 1.9
			after treatment	188.1 ± 88.3	953.3 ± 219.2			25.3 ± 10.5	7.2 ± 1.5	7.80 ± 2.0	13.7 ± 1.6
	Enseki, 2019	AS-R	baseline (median [range])	140 [110, 170]	950 [380, 1310]			23.4 [14.8, 31.5]	6.0 [2.3, 8.1]	4.2 [3.1, —]	
			after treatment	160 [120, 190]	1080 [620, 1290]			28.5 [19.7, 29.2]	6.9 [4.9, 9.2]	7.3 [6.7, 8.2]	
	Tabata, 2018	AS-R	baseline	145.6 ± 30.9				23.7 ± 8.9	5.8 ± 1.1	6.7 ± 1.7	12.5 ± 2.2
			after BPT	144.1 ± 27.5				20.0 ± 10.9	4.3 ± 1.3	4.0 ± 1.4	10.0 ± 2.1
			after bronchodilatation	139.6 ± 32.80				24.8 ± 11.0	6.06 ± 1.4	6.6 ± 2.2	12.5 ± 2.7
Healthy + Asthma	Pasterkamp, 1997	TR	After MCh	Non responders Insp: 529 Exp: 725 Responders Insp: 504 Exp: 589	Non responders Insp: 1533 Exp: 1457 Responders Insp: 1634 Exp: 1477	Non responders Insp: 54,3 Exp: 55,6 Responders Insp: 53,7 Exp: 55,3	Non responders Insp: 46,1 Exp: 52,0 Responders Insp: 44,7 Exp: 48,7				
		Chest (AS-R, AS-L, PI-R, PI-L, AI-R, AI-L, AR)		Non responders Insp: 151-193 Exp: 127-168 Responders Insp: 146-202 Exp: 126-183	Non responders Insp: 490-626 Exp: 314-673 Responders Insp: 573-678 Exp: 383-581	Non responders Insp: 45,3–50,7 Exp: 41,8–47,0 Responders Insp: 45,3–49,6 Exp: 41,7–47,6	Non responders Insp: 19,8–26,3 Exp: 8,7–21,6 Responders Insp: 17,4–26,2 Exp: 9,2–22,2				
		TR	Baseline	Non responders Insp: 593 Exp: 780 Responders Insp: 463 Exp: 566	Non responders Insp:1498 Exp: 1399 Responders Insp: 1583 Exp: 1354	Non responders Insp: 52,2 Exp: 53,2 Responders Insp: 53,3 Exp: 55,6	Non responders Insp: 46,1 Exp: 52,7 Responders Insp: 44,6 Exp: 49,5				
		Chest (AS-R, AS-L, PI-R, PI-L, AI-R, AI-L, AR)		Non responders Insp: 138-179 Exp: 125-157 Responders Insp:142-181	Non responders Insp: 406-538 Exp: 293-833 Responders Insp: 403-555	Non responders Insp: 48,7–53,4 Exp: 39,7–46,6 Responders Insp: 47,2–52,4 Exp: 39,0–45,0	Non responders Insp: 19,9–27,8 Exp: 6,3–20,7 Responders Insp: 17,1–27,9 Exp: 4,9–18,0				

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Table A (*continued*)

Health Status	Autor, Year	Location		F50 (Hz)	F99 (Hz)	P low Freq (dB) at 100–200 Hz	P high Freq (dB) at 200–400Hz)	Spectral slope on 600–1200 Hz (dB/oct)	RPF50	RPF75	A3/AT
				Exp: 115-167 100–800	Exp: 397-616						
Bronchiolitis	Sanchez, 2005	AI-R, AI-L									
7 days post LRTI	Shioya, 2018	AS-R	All participants		Median range: 640 to 900			Median range: 6,3 to 13,5	Median range: 6.2 to 7.7	Median range: 5.8 to 8.0	Median range: 11.1 to 12.7
			wheezing vs not median [range]		690 [260, 1260] vs 675 [280, 1460]			6.4 [2.1, 16.2] vs 6.4 [2.3, 18.7]	6.7 [2.1, 14.3] vs 6.3 [2.3, 18.7	6.9 [1.8, 17.0] vs 6.6 [2.5, 18.0]	12.7 [5.4, 19.9] vs 12.4 [7.0, 20.1]
			RSv vs not		900 [400, 1340] vs 670 [260, 1460]			27.0 [14.5, 54.5] vs 27.1 [-1.7, 66.5]	7.1 [3.0, 11.2] vs 6.4 [2.1, 18.7]	6.4 [3.4, 14.2] vs 6.6 [1.8, 18.0]	12.4 [7.2, 20.1] vs 12.5 [5.4, 19.9]
			hospitalization vs not		815 [370, 1260] vs 680 [260, 1460]			27.0 [19.6, 33.8] vs 27.1 [-1.7, 66.5]	6.8 [5.1, 7.7] vs 6.4 [2.1, 18.7]	5.8 [5.6, 7.4] vs 6.7 [1.8, 18.0]	11.1 [7.2, 12.0] vs 12.6 [5.4, 20.1]
			allergy vs not		720 [380, 970] vs 680 [260, 1460			31.5 [20.9, 64.9] vs 26.7 [-1.7, 66.5]	7.7 [4.1, 12.9] vs 6.3 [2.1, 18.7]	8.0 [4.3, 14.1] vs 6.5 [1.8, 18.0]	12.1 [9.9, 16.7] vs 12.5 [5.4, 20.1
			atopic dermatitis vs not		730 [350, 1130] vs 670 [260, 1460]			30.8 [3.9, 66.5] vs 26.7 [-1.7, 66.4]	7.6 [3.2, 16.5] vs 6.2 [2.1, 18.7]	8.0 [3.4, 18.0] vs 6.5 [1.8, 17.4]	12.3 [8.0, 17.0] vs 12.6 [5.4, 20.1]
			family history vs not		700 [280, 1340] vs 640 [260, 1460]			27.0 [-1.7, 66.5] vs 27.2 [-1.7, 66.4]	6.4 [2.1, 16.2] vs 6.4 [2.3, 18.7]	6.9 [2.5, 18.0] vs 6.3 [1.8, 16.8]	12.7 [7.0, 20.1] vs 11.9 [5.4, 19.0]

Legend: Data is presented as mean ± standard deviation or median [interquartile range], unless otherwise stated; AI - anterior inferior; AM-anterior middle; AS - anterior superior; AX-axilla; A3-third area under the curve; AT-total area under the curve of 100 Hz to the highest frequency of the of the of the dBm power spectrum; BPT-bronchial provocation test; CG-control group; CR-crackle; F50, F99 - frequencies of 50, 99% respectively of the spectral sound measured (Hz); Freq-frequency; GINA-global initiative for asthma; IG-intervention group; L-left; MCh-methacholine challenge; P-power; PI-posterior inferior; PS-posterior superior;; R-right; R/L-right to left; RPF50 or 75-ratio power/frequency at 50 or 75% of the highest frequency of the dBm power (dBm/Hz); R-right; RSV-respiratory syncytial virus; TR-trachea; SALB-salbutamol.

Table B
Synthesis of adventitious respiratory sound - wheezes measurements (n=12).

Health Status	Author Year	Location	Timing	Presence of wheezes	WH%	Lowest Freq of WH (Hz)	Higher Freq of WH (Hz)	Duration of WH (ms)
Healthy	Fenton 1985	TR	Inspiratory Expiratory		0.0 ± 0.0 0.0 ± 0.0			
	Murayama 2019	AS-R	Both	1.6%				
Bronchiolitis	Beck 2007	AX-R, AX-L, AI-R, AI-L	Total		5.47 ± 3.26 to 11.9 ± 4.50			
	Sanchez 2005	AI-R, AI-L	Sinusoidal WH Complex WH			252 ± 10 162 ± 16		250 ± 22 35 ± 11
	Faber 2015	TR, AS-R, AS-L, AI-R, AI-L	Pre nebulization Post nebulization	33% 18%	3.4 ± 3.84 2.0 ± 2.7499			
	Sanchez 2002 Tal 1991	AI-R, AI-L	WH CR + WH	11% 11%	53% 47%	252 ± 10 162 ± 16		250 ± 22 35 ± 11

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Table B (*continued*)

Health Status	Author Year	Location	Timing	Presence of wheezes	WH%	Lowest Freq of WH (Hz)	Higher Freq of WH (Hz)	Duration of WH (ms)
		AS-R or PS-R or PS-L	ΔWH% > 10% (pre-post salbutamol)		47 ± 26% to 20 ± 25%		230 ± 5 to 255 ± 1	
			ΔWH% < 10% (pre-post salbutamol)		31% ± 13%–38% ± 12%		271 ± 64 to 206 ± 21	
Asthma	Fenton 1985	TR	Inspiration		0 to 24.7 ± 25.9		630 ± 80	
			Expiration		0 to 21.6 ± 25.3		630 ± 110	
	Mazic 2003	TR, AI-R	normal breathing (NB)				400	100
			forced breathing (FB)				352.5 ± 82.3 [250;460]	200 ± 93.5 [100;350]
			normal and forced breathing (FB)				380 ± 0.0	250 ± 0.0
	Malmberg 1994	AI-R, AI-L TR				175	350 1200	
Healthy + Asthma	Rietveld 1999	TR	PEF ≥20%	18.30%				
			PEF<20%	6.60%				
			no decrease on PEF	0%				
Recurrent wheezing	Sanchez 2002	AI-R, AI-L	only WH	94%				
			WH and CR	6%				
Non-specified health status	Bokov 2016	Mouth	with WH		4.6 ± 3.1			151 ± 39
			without WH		6.1 ± 4.6			148 ± 32
		TR	with WH		1.6 ± 1.4			95 ± 40
			without WH		2.2 ± 2.7			90 ± 48
Atelectasis	Adachi 2016	AS-R, AS-L	Pre-Post RPT	−7 (53.8%)				
Asthma, CF, LRTI or pre-school wheezes	Kevat 2017	PS-R, PS-L, PI-R, PI-L	inspiratory					190 (40;400)
			expiratory					290 (310;120)
	Murayama 2019	AS-R	Both	8.7%				

Legend: Data is presented as mean ± standard deviation or median [interquartile range], unless otherwise stated; AI - anterior inferior; AM-anterior middle; AS - anterior superior; AX-axilla; BPT-bronchial provocation test; CG-control group; CR-crackle; F50 - frequencies of 50% of the spectral sound measured (Hz); Freq-frequency; IG-intervention group; L-left; MCh-methacholine challenge; P-power; PI-posterior inferior; PS-posterior superior; R-right; R/L-right to left; RPF50 or 75-ratio power/frequency at 50 or 75% of the highest frequency of the dBm power (dBm/Hz); RPT-respiratory physical therapy; RSV-respiratory syncytial virus; TR-trachea; WH%-wheeze occupation rate; WH-wheeze.

Table C
Synthesis of adventitious respiratory sound - crackles measurements (n=4).

Health Status	Author, Year	Location	Situation	Presence of crackles	Nº of Crackles per breath cycle	Duration (ms)
Bronchiolitis	Beck 2007	AX-R, AX-L, AI-R, AI-L	Per breath cycle		1.14 ± 0.23 to 2.48 ± 0.97	
Right middle lobe atelectasis	Adachi 2016	AS-R, AS-L	Pre-Post RPT	−4 (30.8%)		
Asthma, CF, LRTI or pre-school wheezes	Kevat 2017	PS-R, PS-L, PI-R, PI-L				10 to 15 (6–20)
Recurrent wheezing	Sanchez 2002	AI-R, AI-L	WH and CR	6%		

Legend: Data is presented as mean ± standard deviation or median [interquartile range], unless otherwise stated; AI - anterior inferior; AM-anterior middle; AS - anterior superior; AX-axilla; CR-crackle; L-left; PI-posterior inferior; PS-posterior superior; R-right; R/L-right to left; RPT-respiratory physical therapy; WH-wheeze.

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