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1 **TITLE:**

2 **Computerized adventitious respiratory sounds as outcome measures for respiratory**
3 **therapy: a systematic review**

4 **ARS as outcome measures for respiratory therapy**

5 Alda S. P. D. Marques, PhD[1,2], Ana L. A. Oliveira[1], PT, Cristina I. O. Jácome, MSc[1, 3]
6

7 1 School of Health Sciences, University of Aveiro (ESSUA), Aveiro, Portugal

8 2 Unidade de Investigação e Formação sobre Adultos e Idosos (UniFAI), Porto, Portugal

9 3 Research Centre in Physical Activity, Health and Leisure, Faculty of Sports, University of
10 Porto, Portugal

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20 drafted the manuscript and revised it critically for important intellectual content.
21

22 **Corresponding author:** Alda Marques, School of Health Sciences, University of Aveiro
23 (ESSUA), Agras do Crasto - Campus Universitário de Santiago, Edifício 30, 3810-193 Aveiro,
24 Portugal. Telephone: 00351 234 372 462. Email: amarques@ua.pt

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Abstract

Introduction: There is a need to develop simple, non-invasive and sensitive outcome measures for respiratory therapy. Adventitious respiratory sounds (i.e., crackles and wheezes) can be objectively characterized with computerized respiratory sound analysis and have been shown to contribute for diagnosis purposes however; their potential to be used as outcome measures is unknown. Thus, this systematic review synthetizes the evidence on the use of computerized adventitious respiratory sounds as outcome measures.

Methods: The Web of knowledge, MEDLINE, EMBASE and SCOPUS databases were searched. Reviewers independently selected studies according to the eligibility criteria. Effect sizes and 95% confidence intervals were computed.

Results: Twelve studies with different designs (observational (n=3), quasi-experimental (n=7) and randomized controlled trial (n=2)) were included. Eight studies were conducted with adults and four with children. Most studies explored only one type of adventitious respiratory sound. For wheezes, the occupation rate seemed to be the most promising parameter to be used as an outcome measure, with high/medium effect sizes (from 0.62 to 1.82). For crackles, the largest deflection width showed high effect sizes (1.31 and 1.04) however, it was only explored in one study. Crackle number and two cycle duration presented conflicting information, with high/poor effect sizes depending on the study.

Conclusion: Specific variables of each adventitious respiratory sound detected and characterized by computerized respiratory sound analysis showed high effect sizes and thus, potential to be used as outcome measures. Further research with robust study designs, larger samples, both of children and adult populations, and following CORSA guidelines are needed to build evidence base knowledge on this topic.

Key words: computerized respiratory sound analysis; respiratory sounds; adventitious respiratory sounds; wheezes; crackles; outcome measure

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Introduction

Respiratory diseases are a major cause of societal, health and economic burden worldwide[1]. Therefore, in the last decade, significant research efforts have been dedicated to improve early diagnosis and routine monitoring of patients with respiratory diseases to allow timely interventions. However, this has been found to be highly challenging with the available respiratory measures (e.g., spirometry, blood gas analysis, imaging techniques), since they are commonly affected by patient's motivation and cooperation, are not always available in all clinical settings and are expensive [2, 3].

Computerized respiratory sound analysis, which consists of recording patients' respiratory sounds with an electronic device and analyzing them based on specific signal characteristics: is a simple, objective and non-invasive method to detect and characterize adventitious respiratory sounds (ARS), i.e., crackle (CR) and wheeze (WH). ARS provide crucial information on respiratory dysfunction[4] and changes in their characteristics (intensity, duration, timing, etc.) might inform the clinical course of respiratory diseases and treatments[5, 6]. Through the use of computerized respiratory sound analysis, ARS have been found to be a more sensitive indicator, detecting and characterizing the severity of the respiratory disease before any other measure[7]. Thus, this approach through the objective data collection and management, generation of permanent records of the measurements made with easy retrievability and through graphical representations, assists the diagnosis and monitoring of patients with respiratory diseases[8-11].

However, research on this topic has been focusing on the use of computerized respiratory sound analysis as a diagnostic aid[12] and the findings reporting its potential to be used as an outcome measure, i.e., to monitor respiratory treatments, are widespread in the literature. Thus, this systematic review synthetizes the evidence on the use of computerized ARS as outcome measures.

Methods

Search strategy

An electronic literature search was performed from December 2012 to January 2013 in Web of knowledge (1970-2012), MEDLINE (1948-2012), EMBASE (1974-2012) and SCOPUS (1960-2013) databases. Search terms were based on a combination of the following keywords: monitor* OR "computerized analyses" OR "digital auscultation" OR "electronic auscultation" OR "automatic auscultation" OR "acoustic signal processing" AND "added lung sounds" OR "abnormal lung sounds" OR "adventitious lung sounds" OR "adventitious respiratory sounds" OR crackle* OR wheez*. The search terms were limited to titles and abstracts. The reference lists of the selected articles were scanned for other potential eligible studies. Additionally, a weekly update was conducted until June 2013. This systematic review is reported according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[13].

Eligibility criteria

Articles were included if 1) they detected and characterized ARS with computerized respiratory sound analysis before and after an intervention on adults or children; 2) were experimental, quasi-experimental or observational studies; 3) were full papers published as original articles or in conference proceedings and 4) were written in English, Portuguese, Spanish or French. Articles were excluded if the study was conducted with animals or assessed ARS with computerized respiratory sound analysis only at one specific moment in time. Book chapters, review papers, abstracts of communications or meetings, letters to the editor, commentaries to articles, unpublished work and study protocols were not considered suitable and, therefore, were also excluded from this review.

Study selection

Duplicates were first removed. Then, the title, abstract and keywords were analyzed to assess the type and relevance of the publication for the scope of the review. Finally, the full-text of potentially relevant articles was independently screened for content by the three reviewers to decide its inclusion in the review. Reviewers resolved disagreements by consensus.

Data extraction

Data from the included articles were extracted in a structured table-format, i.e.,: first author's last name and year of publication, type of study, participants, intervention, data collection protocol, recording device, data analyses, ARS outcome and findings.

Quality assessment

The quality of the included studies was assessed with the checklist created by Downs and Black[14]. The checklist provides a list of 27 questions to measure study quality, split into five sections: reporting (ten items); external validity (three items); internal validity – bias (seven items); internal validity – confounding (seven items) and power (one item). Similarly to previous systematic reviews[15, 16], the scoring for question 27 - dealing with statistical power, was simplified to a choice of awarding either 1 point or 0 points, depending on whether there was sufficient power to detect a clinically important effect. Downs and Black score ranges were grouped into the following 4 quality levels: excellent (26 –28), good (20 –25), fair (15–19), and poor (≤14)[15, 16]. The risk of bias assessment was carried out by two independent reviewers. Disagreements between reviewers were resolved by reaching a consensus through discussion.

Data analysis

To determine the consistency of the quality assessment performed by the two reviewers, an inter-rater agreement analysis using the Cohen's kappa was performed. The value of Cohen's kappa ranges from 0 to 1 and can be categorized as slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) or almost perfect (≥0.81) agreement[17]. This statistical analysis was performed using PASW Statistics (version 18.0, SPSS Inc., Chicago, IL). When quantitative pooling was appropriate the effect sizes together with the 95% confidence intervals (95% CI) were computed for the outcomes of interest. The effect sizes (ES) were interpreted as low (0.20), medium (0.50) and high (0.80) effect magnitudes[18]. This quantitative data analyses were performed using the meta-analysis software Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, New Jersey)[19].

Results

Study selection

The database search identified 1224 records. After duplicates removal, 900 records were screened for relevant content. During the title, abstract and keyword screening, 876 articles were excluded. The full-text of the 24 potentially relevant articles was assessed and 18 articles were excluded due to the following reasons: ARS detection was performed with standard auscultation (n=2) or manual annotation (n=4), ARS automatic detection occurred only in one specific time-point to validate algorithms (n=5), did not provide data on ARS (n=3) and an intervention was absent (n=4). Six original articles were included in the review. The search for relevant articles within the reference list of the selected articles retrieved 6 studies which were also included.

(insert figure 1 about here)

Quality assessment

The articles included in this review scored 10 to 21 on the Downs and Black checklist, with a mean of 14.42±0.93 (Table 1). Results of the risk of bias assessment indicated that seven (64%) studies had poor quality, four had fair quality and one good quality. Studies scored particularly poor on the following items: description of confounders, sample representativeness, patient blinding, outcome assessor blinding, recruitment, randomization, adjust for confounding factors in the analysis and power to detect outcomes that are clinically important. The agreement between two authors was almost perfect (k=0.825; 95% CI 0.758-0.885; p=0.001).

(insert table 1 about here)

Study characteristics

The majority of the included studies were quasi-experimental[5, 20-25], three were observational[26-28] and two were randomized controlled trials[29, 30]. Ten studies recruited patients receiving specialized care and two during hospital admission[24, 27]. A total of 275 subjects (n=126; 45.8% male) participated in the included studies, 47 were healthy subjects and 208 had respiratory conditions (Asthma (n=84), Pneumonia (n=11), Cystic fibrosis (n=23), Chronic Obstructive Pulmonary Disease (COPD) (n=6), prolonged cough (n=28), Bronchiolitis (n=27), Bronchiectasis (n=23) and Lower Respiratory Tract Infection (LRTI) (n=26)). Eight studies were

conducted with adults (n=167; 60.7%; age range 21-73 years old)[5, 21, 24-29] and four with children (n=108; 39.3%; age range 4 months - 18 years old)[20, 22, 23, 30].

The interventions of most studies consisted of pharmacotherapy[20-30], only two studies combined pharmacotherapy with respiratory physical therapy[5, 29]. The respiratory physical therapy consisted mainly in active cycle of breathing techniques[5, 29], but also breathing retraining techniques; incentive spirometry; thoracic mobility, expansion and flexibility exercises and aerobic training[29]. In almost all studies, the respiratory sounds were recorded in more than one chest location however, in three studies recordings were performed exclusively in the trachea[21, 25, 26]. Only the three more recent studies, acquired the respiratory sounds following the Computerized Respiratory Sound Analysis (CORSA) guidelines for short-term acquisition[5, 28, 29]. The recording devices used varied among studies: microphones[21, 24, 25, 27, 29], piezoelectric sensors[20, 22, 23, 26, 30] and electronic stethoscopes[5, 28].

Algorithms based on Fast Fourier Transformation were the most used to automatically detect ARS. Two studies used an algorithm based on Short-Time Fourier transformation[28, 29] and one used a modification of the algorithm proposed by Shabtai-Musih et al.[31] and Homs-Corbera et al[25, 32]. A total of nine studies analyzed WHs (3 were conducted in children), two analyzed CRs[5, 27] and one both WHs and CRs in children[30]. Two studies detected breathing cycles automatically, one used an analogous method reported by Qiu et al[5, 33] and the other used the Huq and Moussavi algorithm[30, 34]. Only three studies considered the breathing phases (inspiration and expiration) in the analysis of the ARS[26, 27, 29].

(insert table 2 about here)

Synthesis of the results

Wheezes

Presence

The presence of WHs was used to identify a bronchial response during bronchial provocation tests in two studies conducted with children[20, 22]. Sanchez et al. (1993) used concentrations of

methacholine and found that WHs had 50% sensitivity and 100% specificity to detect bronchial hyperreactivity[20]. Bentur et al. (2004) observed that WHs were detected after a mean adenosine concentration of 15.6mg/ml[22]. Both studies verified that WHs were feasible to assess bronchial reactivity.

Number

Two studies investigated the number of WHs in adults. Oliveira et al. (2013) found a significant increase in the number of WHs after 3 weeks of standard medical treatment (6 vs. 14.8; p=0.03; ES=4.38) in patients with LRTI[28]. A similar result, but not significant, was found in subjects with stable asthma after terbutaline inhalation (ES=0.34), however in healthy subjects and subjects with non-stable asthma a non-significant decrease was observed (ES=-0.10 and ES=-0.012, respectively)[25].

Frequency

The frequency of WHs was investigated in four studies conducted with adults[21, 25, 28, 29]. After terbutaline inhalation, the frequency of WHs significantly decreased in patients with asthma (ES=-0.15), COPD (ES=-0.21) and in healthy subjects (ES=-0.28)[21]. Similar, however non-significant, results were found with the same intervention in healthy subjects (ES=-0.18) and subjects with non-stable asthma (ES=-0.24)[25]. In subjects with stable asthma (ES=0.01)[25] and LRTI (ES=-0.06)[28] the frequency remained approximately the same. Dinis et al. (2013) investigated the effect of respiratory physical therapy in subjects with LRTI and observed a non-significant increase in the frequency of inspiratory and expiratory WHs in both experimental (ES=0.73 and ES=0.04, respectively) and control groups (ES=0.97 and ES=0.97, respectively)[29].

Occupation rate

This parameter, which is the proportion of the respiratory cycle occupied by WHs**,** was explored in studies conducted with children and adults. In three studies the wheeze occupation rate (WH%) was used to analyze the effect of pharmacotherapy[24, 25, 30]. A non-significant reduction in WH% during the night in the group of subjects administered with long-acting sympathomimetic

agent (ES=-1.9) was found; whereas in the placebo group, a significant increase was observed (ES=1.15)[24]. In a study conducted with infant viral bronchiolitis, WH% also decreased 10 minutes after the administration of epinephrine (ES=-1.09); however it increased in the group of children administered with albuterol (ES=1.27)[30]. Nevertheless, no significant differences were found between or within groups. When exploring monophonic and polyphonic WH% significant change was also not found however, low effect sizes in non-stable and healthy subjects and medium effect sizes in subjects with stable asthma (ES=-0.54) were found[25]. A significant decrease in inspiratory and expiratory WH% was found after 3 weeks of pharmacotherapy plus respiratory physical therapy (ES=-0.66 (inspiratory); ES=-0.64 (expiratory)) or pharmacotherapy alone (ES=-0.69 (inspiratory); ES=-0.62 (expiratory))[29]. A similar result was found for the nocturnal WH index, calculated from the WH% (after 2 days (ES=-0.61) and after 6 weeks (ES=-0.80)), when monitoring respiratory sounds overnight to assess the effects of montelukast in nocturnal asthma[23].

Duration

Two studies explored this variable when assessing the impacts of pharmacotherapy with adult subjects[26, 28]. In both studies WH duration remained approximately the same pre/post intervention. Only in subjects with moderate and severe obstruction, changes in the duration of WHs after medication were observed[26].

Crackles

Number

Three studies analyzed the number of CRs before and after intervention and no significant differences were found. In two studies, this variable remained approximately the same, with effect sizes ranging from 0.02 to 0.22[5, 27]. In the study of Beck et al., the number of CRs increased (ES=0.58) with albuterol and decreased with epinephrine (ES=-1.65)[30].

Frequency

The CR frequency was analyzed only in one study[27]. The peak frequency increased during inspiration (ES=0.11) and decreased during expiration (ES=-0.47) whereas the upper frequency at -20-dB level decreased in both inspiration (ES=-0.12) and expiration (ES=-0.35). No significant differences were found.

Two cycle duration (2CD), Largest deflection width (LDW) and Initial deflection width (IDW)

Two studies analyzed the 2CD variable; Marques et al. did not show any change from pre to post intervention (ES=0.07)[5] and Piirila showed a non-significant reduction post intervention both in inspiratory (ES=-0.85) and expiratory (ES=-0.83) phases[27]. In the study of Piirila, both LDW and IDW of inspiratory (ES=-1.25 and -0.38) and expiratory (ES=-1 and -0.76) CRs were shorter after the intervention[27].

Timing

Only Piirila explored timing parameters of the CRs related to inspiratory tidal volume and inspiratory and expiratory phases. These parameters were significantly different post intervention (ES from 0.5 to 1.14)

Due to the heterogeneity of the outcome measures used across studies, a meta-analysis was not possible to compute.

Discussion

The main finding of this systematic review was that ARS detected and characterized by computerized respiratory sound analysis show potential to be used as outcome measures in children and adults, as specific variables of each ARS presented high effect sizes. However, the most appropriate variable(s) or variables are yet to be explored.

Most studies (11/12) explored WH presence and characteristics before/after an intervention. Wheeze occupation rate seemed to be the most promising parameter to be used as an outcome measure in children and adults, with medium to high effect sizes varying from 0.62 to 1.9[24, 29]. A strong association between the proportion of the respiratory cycle occupied by WHs and the degree of bronchial obstruction has been widely demonstrated[21-23, 35]. This WH parameter, even

when identified with standard auscultation, has shown to be sensitive to assess the effectiveness of respiratory interventions in children[36, 37]. The WH complexity may also be a variable of interest as the presence of polyphonic WHs indicates a more serious obstruction than monophonic WHs[25] however, this was only explored in one study (ES from 0.24 to 0.54)[25]. Wheeze monitoring has been found to provide more information on the changes of airway obstruction than measurements of pulmonary function[24], such as the percentage predicted of FEV_1 in people with asthma[26]. Thus, WHs and their variables seem to be a promising objective outcome measure for all populations with a special emphasis on non-collaborative populations such as children, people with dementia and people in the intensive care. However, it should be noticed that WHs only occur when there is a flow limitation (but flow limitation is not necessarily accompanied by WHs), that reaches a critical value, called flutter velocity[38]. Thus, when there is not enough flow to generate WHs, WHs parameters will not be useful despite the presence of the respiratory problem. The complementary information provided by CRs is therefore, crucial.

Crackles are assumed to be caused by the sudden opening of abnormally closed airways[39-42], and their parameters provide essential information about the function and structure of the tracheobronchial tree[41], e.g., CR recording during mechanical ventilation has been considered a simple method to monitor lung recruitment-derecruitment[43]. However, CR variables have been explored as outcome measures in only three studies[5, 27, 30]. From the limited evidence available, LDW seemed to be the most valuable parameter to be used as an outcome measure due to its high effect sizes (1 and 1.25)[27]. Hoevers and Loudon (1990) had already found that LDW seemed to be a better measure than IDW or 2CD when differentiating between coarse and fine CRs[44]. However, LDW was also the variable less explored among studies. Conflicting information was found for the number of CRs and 2CD. The number of CRs had low effect sizes reported in Piirila (0.14 and 0.22)[27] and in Marques et al. (0.02)[5] studies, and medium/high effect sizes in Beck et al. (0.74 and 1.65)[30]. High (0.83 and 0.85)[27] and low (0.07)[5] effect sizes were also found for the variable 2CD. The timing of CRs (ES 0.5 to 1.14) also showed to be sensitive to the clinical course of pneumonia[27] and has been described as a sensitive parameter to discriminate respiratory diseases[45]. However, similarly to LDW limited research has been conducted considering this parameter as an outcome measure. At this point in time it is difficult to provide any recommendations on which CR's variable(s) are more adequate to be

used as an outcome measure to monitor respiratory interventions. These limited and conflicting data may be a result of the different respiratory sound acquisition sensors (which differ in their acoustic sensitivity to capture CRs waveforms), filtering and analysis methods used across studies[46, 47]. Since CRs show potential for diagnosis purposes but also as an outcome measure for respiratory treatments in different clinical/research contexts, these procedures need to be standardized. This will allow comparisons among different studies and improve the understanding of CRs' mechanisms and acoustic characteristics.

The study of both main types of ARS is essential to gather complementary information about the tracheobronchial tree. This information may help health professionals to conduct more accurate diagnosis and enhance their understanding about the respiratory system responses to treatments. However, only one study analyzed both types of ARS as an outcome measure in a study conducted with children[30]. Thus, the study of computerized ARS is an exciting area where much research is needed to develop knowledge for diagnosis and monitoring of patients but also to be used as a non-invasive, objective and reliable outcome measure for treatments.

The level of evidence that can be drawn at this moment in time from this systematic review is considerably weak due to the 1) small sample sizes; 2) distinct respiratory therapies and doses implemented and 3) different ARS variables used in the included studies. The large variety of acquisition methods used is an issue added to the list of difficulties when comparing results across studies. A BIOMED 1 Concerted Action project entitled CORSA, funded by the European Community, developed guidelines for research and clinical practice in the field of respiratory sound acquisition and analysis[4, 9, 48]. The CORSA project group produced guidelines on the definitions of medical/technical terms used in pulmonary acoustics; environmental conditions; patient management procedures; acquisition, pre-processing, digitization and analysis of respiratory sounds; and also about publishing the results of research[4, 9, 48]. These international guidelines have been available since 2000, however from the 9 studies conducted after this year, only 3 followed the acquisition procedures recommended by CORSA. Regarding the analysis methods, algorithms based on Fast Fourier Transformation were the most used, which is in accordance with the CORSA recommendations. Future research, with improved study designs, larger samples, both of children and adult populations, and following the CORSA

guidelines, should be conducted to explore the ARS response to respiratory therapies. This will facilitate the comparison of results from different studies, promote research into the development of standardized respiratory sound acquisition equipment and analysis and finally enhance the understanding of computerized ARS as well as their use as an outcome measure.

Conclusion

Specific variables of each ARS detected and characterized with computerized respiratory sound analysis showed high effect sizes and thus may have potential to be an objective, reliable and non-invasive outcome measure for respiratory therapy in children and adults. Further research exploring the ARS response to different respiratory therapies are needed to enhance the understanding of computerized ARS and their clinical use not only for the diagnosis purposes but also for monitoring patients and treatments.

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1 Figure captions

2 Figure 1 - PRISMA Flowshart of the included studies.

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Table 1 - Quality assessment score for selected studies based on the Downs and Black checklist.

Study (year)	Reporting MS=11	External validity MS=3	Internal validity – bias MS=7	Internal validity - confounding MS=6	Power MS=1	Total Score
Baughman & Loudon (1988)	5	0	6	1	0	12
Piirila (1992)	7	1	3	2	0	13
Sanchez et al. (1993)	6	1	4	0	0	11
Fiz et al. (2002)	7	0	5	0	0	12
Bentur et al. (2003)	8	0	4	1	0	13
Bentur et al. (2004)	8	2	5	2	1	18
Cortes et al. (2005)	6	1	1	2	0	10
Fiz et al. (2006)	8	0	5	3	0	16
Beck et al. (2007)	8	1	7	5	0	21
Marques et al. (2012)	8	1	5	2	0	16
Oliveira et al. (2013)	7	1	4	2	0	14
Dinis et al. (2013)	8	1	5	3	0	17

MS, maximum score.

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Table 2 – Characteristics of the adventitious respiratory sounds pre-post intervention.

Study (Year)	Type of study	Participants	Intervention	Data collection protocol	Recording Device	Data Analyses	ALS outcomes	Findings
Baughman & Loudon (1988)	Quasi-Experimental	10 subjects with nocturnal asthma	One night Placebo One night Long-acting β_2-sympathomimetic agent – procaterol (0.1mg)	Respiratory sound recordings: - night monitoring of wheezing after intervention at 12am and at 4am; - 6 segments of 5 minutes recordings at each assessment; - microphone of an accelerometer placed over the cricopharynx; - stethoscope over the right anterior chest.	Modified stethoscope air-coupled to a microphone.	**WHs** detection: FFT Analyses for the presence/ absence of a peak at a frequency 150-1,000Hz.	**WH%**	**Placebo** **WH%**: 12AM 18±5.3%; 4AM 24.8±6.4%; p<0.05 (ES=1.15) **Procaterol** **WH%**: 12AM 23.2±6.9%; 4AM 11.8 ±4.0% (ES=-1.9)
Piirila (1992)	Observational	11 subjects with pneumonia 21-71yrs 6M:5F	Standard medical treatment	Respiratory sound recordings: - 2.2±1.1 days after hospital presentation and then after 2.7±1.0 days; - subjects in a sitting position, breathing with a maximum flow of 1L/s; - 5 complete respiratory cycles; - basal regions of both lungs.	Air-coupled condenser microphones	CR detection: Phonopneumography FFT TEW Automatic CR counter	**CR:** N IDW 2CD LDW Beginning Duration End point PF Fu Ie	**Inspiratory CR** N: Pre 5±1.9; Post 6± 5.3 (ES=0.22) IDW: Pre1.5±0.2ms; Post 1.4±0.3ms (ES=-0.38) 2CD: Pre 10.1±1.3ms; Post 8.6±2ms (ES=-0.85) LDW: Pre 2.6±0.4ms; Post 2.1±0.4ms; p<0.05 (ES=-1.25) Beginning: Pre 35±16%Vt; Post 53±19%Vt; p<0.01 (ES=1.02) Duration: Pre 35±13%Ti; Post 36±8%Ti (ES=0.09) End point: Pre 72±13%Vt; Post 83±14%Vt (ES=0.81) End point: Pre 69±11%Ti; Post 81±10%Ti; p<0.05 (ES=1.14) PF: Pre 156±46Hz; Post 161±42Hz (ES=0.11) Fu: Pre 437±71Hz; Post 426±106Hz (ES=-0.12)

								Ie: Pre 0.64±0.34V; Post 0.50±0.23V (ES=-0.47) **Expiratory CR** N: Pre 0.8±0.8; Post 0.7±0.14 (ES=-0.14) IDW: Pre1.7±0.4ms; Post1.3±0.6ms (ES=-0.76) 2CD: Pre 11.9±2.4ms; Post 8.1±5.3ms (ES=-0.83) LDW: Pre 3±0.6ms; Post 2.4±0.6ms (ES=-1) Beginning: Pre 56±14%Te; Post 63±14%Te (ES=0.5) Duration: Pre 46±39%Te; Post 22±0%Te (ES=-0.62) End point: Pre 79±23%Te; Post 95±0%Te (ES=0.7) PF: Pre 126±42Hz; Post 109±22Hz (ES=-0.47) Fu: Pre 365±127Hz; Post 327±69Hz (ES=-0.35)
Sanchez et al. (1993)	Quasi-Experimental	EG: 23 children with cystic fibrosis 4-18yrs 14M:9F CG: 18 healthy children 4-16yrs 7M:11F	Methacholine challenge: doubling concentrations of methacholine nebulized for 2 min (start 0.03mg/ml)	Respiratory sound recordings: - 1min after each dose; - spontaneous breathing; - sounds at trachea and posterior right lower lobe recorded simultaneously.	Piezoelectric accelerometers	WHs detection: FFT Based on PF (auditory verification on digital-to-analog playback)	Presence of WHs	WH as an indicator of bronchial hyperreactivity: Se:50% Sp:100%
Fiz et al. (2002)	Quasi-Experimental	EG1: 16 subjects with asthma 53.6±16.3yrs 9M:7F	Inhalation of terbutaline (1mg)	Respiratory sound recordings: - acquired before and 20min after the intervention; - FVC maneuvers; - at the trachea.	Contact microphone	WHs detection: FFT Modified version of the Shabtai-Musih et al. algorithm	WH frequency	**EG1** F: Pre 560.9±140.8Hz; Post 538.4±160.5Hz; p<0.01 (ES=-0.15) **EG2** F: Pre 669.4±250.1Hz; Post 620.6±208.9Hz; p<0.01

		EG2:6 subjects with COPD 58.8±4.9yrs 6M:0F CG: 15 healthy subjects 45.8±12.5yrs 7M:8F						(ES=-0.21) **CG** F: Pre 750.7±175.7; Post 701.6±170.1; p<0.01 (ES=-0.28)
Bentur et al. (2003)	Quasi-Experimental	12 children with asthma 6-14yrs 6M:6F	Montelukast daily (5mg)	Respiratory sound recordings: - overnight (8h) monitoring of wheezing before the intervention (Pre), after 48 hours (Post 1) and after 6 weeks (Post2); - at the trachea, right and left axillae and both posterior bases of the lungs.	Phonopneumography piezoelectric contact sensors connected to an automatic WH detection device	WHs detection: FFT based algorithm	NWI	NWI: Pre 814±898; Post1 318±199; p=0.05 (ES=-0.61) Post2 137±101; p=0.028 (ES=-0.80)
Bentur et al. (2004)	Quasi-Experimental	28 children with prolonged cough 8.3±4.3months 19M:9F	Acoustic Brochial Provocation tests: Nebulized adenosine solutions (start 0.39 mg/ml) inhaled for 2 min; dose doubled at 5min intervals	Respiratory sound recordings: - after each 2 min of inhalation; - records of 30s; - at the trachea, the axilla right, and the axilla left, and both posterior bases of the lungs.	Phonopneumography piezoelectric contact sensors connected to an automatic WH detection device	WHs detection: FFT based algorithm (an auditory audit of the data was performed to verify the detection accuracy)	Presence of WHs	Presence of WHs: -at 15.6±25.2(0.78-100)mg/mL of adenosine concentration - at an adenosine concentration ≤25mg/mL in 85% of the subjects with positive BPT
Cortes et al.	Observational	G1:10 subjects with	Bronchodilator inhalation drug	Respiratory sound recordings: - acquired before and after 20 minutes of	Phonopneumography piezoelectric	WHs detection: Frequency analysis	WH duration	**G1** Inspiration: Post duration similar to Pre duration

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(2005)		asthma (FEV1<50%) 42±17yrs G2: 11 subjects with asthma (50%<FEV1<80%) 42.2±9.7yrs G3: 5 subjects with asthma (FEV1>80%) 29.2±8.7yrs	the intervention; - spontaneous breathing; - 2 records of 120s; - at the trachea.	sensor				Expiration: Post duration similar to Pre duration **G2** Inspiration: Post duration < Pre duration Expiration: Post duration < Pre duration **G3** Inspiration: Post duration similar to Pre duration Expiration: Post duration > Pre duration
Fiz et al. (2006)	Quasi-Experimental	G1: 11 subjects with non-stable asthma 54±15.7yrs 8M:3F G2: 9 subjects with stable asthma 46±12.6yrs 6M:3F CG3: 14 healthy	Bronchodilator inhalation drug (terbutaline - 1mg)	Respiratory sound recordings: - acquired before and after 20 minutes of the intervention; - FVC maneuvers; - at the trachea.	Phonopneumography contact microphone	WHs detection: modification of the algorithm proposed by Shabtai-Musih et al. and Homs-Corbera et al.	WH N F WH% monophonic WH% polyphonic	**G1** N: Pre 13.6±13.3; Post 13.4±19.6 (ES=-0.01) F: Pre 542.7±185.3Hz; Post 527±62Hz (ES=-0.1) WH% monophonic: Pre 52.5±21.6%; Post 47.7±19% (ES=-0.24) WH% polyphonic: Pre 38.2±25.4%; Post 29.9±23.5% (ES=-0.34) **G2** N: Pre 3.5±3; Post 5.5±6.8 (ES=0.34) F: Pre 582.2±226.9Hz; Post 583.3±216.5Hz (ES=0.01) WH% monophonic: Pre 27.0±13.4%; Post 19.4±14.9% (ES=-0.54) WH% polyphonic: Pre 16±21.4%; Post 25.2±30.1%

		subjects 45.4±12.9yrs 8M:6F						(ES=0.34) **G3** N: Pre 2.5±2.1; Post 2.3±1.8 (ES=-0.1) F: Pre 732.6±172.2Hz; Post 701.6±170.1Hz (ES=-0.18) WH% monophonic: Pre 37.1±28.7%; Post 48.2±31.6% (ES=0.37) WH% polyphonic: Pre 15.2±18.9%; Post 10.4±10.9% (ES=-0.29)
Beck et al. (2007)	Experimental	G1: 12 children with infant viral bronchiolitis 4.9±0.8months 4M:8F G2: 15 children with infant viral bronchiolitis 4±1.35months 4M:11F	G1: Nebulized epinephrine (1mg diluted with 2ml of 0.9% saline) G2: Nebulized albuterol (2.5mg diluted with 2.5ml of 0.9% saline)	Respiratory sound recordings: -performed 5min prior to (pre), 10min and 30min post treatment (post1 and post2); - spontaneous breathing; - 5 complete respiratory cycles; - at the right and left axillae and posterior bases of the lungs.	Phonopneumography piezoelectric contact sensors connected to an automatic WH detection device	WHs detection: FFT based algorithm CRs detection: CR counter algorithm (to verify accuracy, segments underwent manual auditory analysis)	WH% CR nBC	**G1** WH%: Pre 9.1±3.4%; Post1 5.47±3.26% (ES=-1.09); Post2 7.1±3.63% (ES=-0.57) CR nBC: Pre 1.88±0.59; Post1 2.48±0.92 (ES=0.74); Post2 2.26±0.7 (ES=0.58) **G2** WH%: Pre 5.5±3.08%; Post1 9.11±2.52% (ES=1.27); Post2 11.9±4.5% (ES=1.61) CR nBC: Pre 1.74±0.42; Post1 1.14±0.23 (ES=-1.65); Post2 1.31±0.33 (ES=-1.12)
Marques et	Quasi-	23 subjects	Single physical	Respiratory sounds recordings:	Electronic	CRs detection:	CRs:	nBC: Pre 4.14±2.31; Post 4.18±2.25 (ES=0.02)

al. (2012)	Experimental	with bronchiectasis 25-73yrs 9M:14F	therapy treatment with ACBT	-before and after the treatment; - spontaneous breathing; - 3 recordings of 25s over each chest location - following the CORSA guidelines for short-term acquisition.	stethoscope connected to a laptop	Vannuccini et al. algorithm BC detection: analogous method to that by Que et al. plus manual adjustment of the detection thresholds	nBC 2CD	2CD: Pre 11.8±1.5ms; Post 11.9±1.54ms (ES=0.07)
Oliveira et al. (2013)	Observational	6 subjects with LRTI 33-63yrs 3M:3F	Standard medical treatment (antibiotics)	Respiratory sounds recordings: -within 24 hours of hospital presentation and after treatment; - spontaneous breathing; -3 recordings of 25s over each chest location -following the CORSA guidelines for short-term acquisition.	Electronic stethoscope connected to a laptop	WHs detection: Taplidou and Hadjileontiadis algorithm based on Short-time FFT	WHs: N F Duration	N: Pre 6±0.9; Post 14.8±2.3; p=0.03 (ES=4.38) F: Pre 365±37Hz; Post 363±29.1Hz (ES=-0.06) Duration: Pre 0.21±0s; Post 0.22±0s (ES=0.11)
Dinis et al. (2013)	Experimental	CG: 11 subjects with LTRI 52.9±18.3yrs 4M:7F EG: 9 subjects with LTRI 49.9±23.2yrs	CG: Standard medical treatment (antibiotics) EG: Standard medical treatment + Respiratory physical therapy (3*week; ACBT, breathing	Respiratory sounds recordings: - within 24 hours of hospital presentation and after treatment; - spontaneous breathing; -3 recordings of 20s; -following the CORSA guidelines for short-term acquisition.	Modified analogue stethoscopes connected to a laptop	WHs detection: Taplidou and Hadjileontiadis algorithm based on Short-time FFT BC detection: Huq and Moussavi automatic	WHs: WH% F	**CG** Inspiration WH%: Pre 11.1±14.8%; Post 2.2±6.2%; p<0.001 (ES=-0.69) F: Pre 241.3±60.1Hz; Post 415.5±201.1Hz; p=0.195 (ES=0.97) Expiration WH%: Pre 11.3±13.2%; Post 4.1±7.7%; p<0.001 (ES=-

	6M:3F	retraining; incentive spirometry; thoracic mobility, expansion and flexibility exercises; aerobic training)	respiratory phase detector using tracheal sounds	0.62) F: Pre 221.2±85.6Hz; Post 396.8±208.1; p=0.243 (ES=0.97) **EG** Inspiration WH%: Pre 9.2±14.1%; Post 0.4±1.9%; p<0.001 (ES=-0.66) F: Pre 360.3±221.1Hz; Post 140.2±153.1Hz; p=0.555 (ES=0.73) Expiration WH%: Pre 10.5±15.3%; Post 1.9±5.4%; p<0.001 (ES=-0.64) F: Pre 423.2±168.6Hz; Post 432.8±269.1Hz; p=0.915 (ES=0.04) **Post CG vs Post EG** Inspiration WH%: 2.2±6.2%; 0.4±1.9%; p=0.019 (ES=0.37) Expiration WH%: 4.1±7.7%; 1.9±5.4%; p=0.061 (ES=0.33)

Data are presented as mean±standard deviation

2CD - two cycle duration; ACBT – active cycle of breathing techniques; BC – breathing cycle; BPT – bronchial provocation test; CG – control group; CORSA - computerized respiratory sound analysis; CR – crackle; EG – experimental group; ES – effect size; FFT – fast fourier transformation analysis; F- frequency; Fu - upper frequency at - 20-dB level; FVC- forced vital capacity; IDW - initial deflection width ; Ie - effective intensity; N – number; nBC – number per breathing cycle; NWI - nocturnal wheeze index; PF – peak frequency; Se – sensitivity; Sp – specificity; TEW - time-expanded waveform; WH - wheeze; WH% - wheeze occupation rate.

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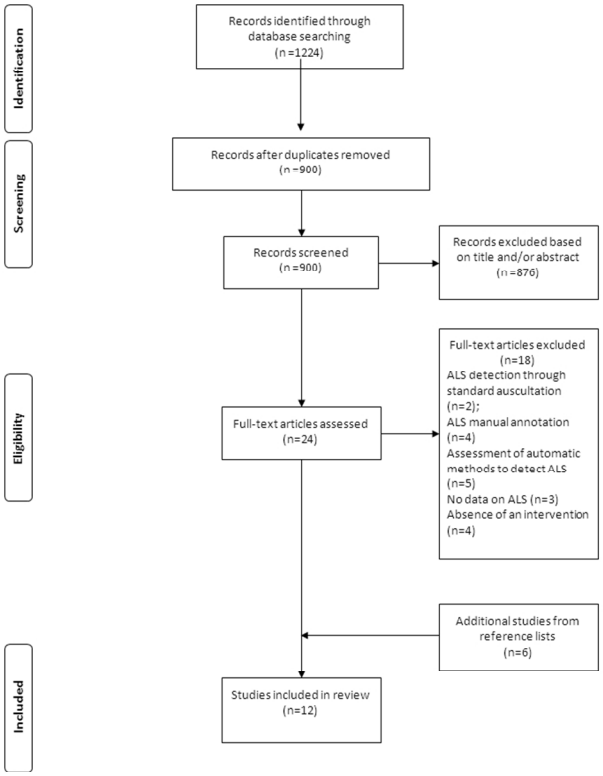

PRISMA Flowshart of the included studies.
300x300mm (96 x 96 DPI)